

**Old, similar, or new: Hippocampal-dependent pattern separation performance in
fibromyalgia**

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Author Note

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Abstract

In addition to chronic musculoskeletal pain, people with fibromyalgia often have memory deficits. Pattern separation is a neurological process that may be related to the memory deficits observed in people with fibromyalgia. Greater hippocampal activation has been associated with pattern separation deficits outside of fibromyalgia and has been observed in people with fibromyalgia. However, the relationship between hippocampal activation and pattern separation deficits in people with fibromyalgia is still unclear. Thus, this study aimed to examine the relationship between hippocampal activation and pattern separation in fibromyalgia. We hypothesized that participants with fibromyalgia would have worse pattern separation performance and greater hippocampal activation compared to healthy controls and that greater hippocampal activation would be correlated with worse pattern separation performance in participants with fibromyalgia. Sixteen participants (five with fibromyalgia and 11 healthy controls) completed the Mnemonic Similarity Task (MST) during functional magnetic resonance imaging (fMRI) scanning and were included in the final analyses. We observed that participants with fibromyalgia had worse pattern separation performance and greater hippocampal activation compared to healthy controls. Further, worse pattern separation performance was correlated with greater hippocampal activation in participants with fibromyalgia. While these findings are preliminary, they suggest that people with fibromyalgia still show pattern separation deficits, even when the hippocampus is working harder.

Keywords: fibromyalgia, pattern separation, hippocampus, memory

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Fibromyalgia is a chronic pain condition with a lifetime prevalence of 6.4% in the United States, with 7.7% of females and 4.9% of males diagnosed in their lifetime (Queiroz, 2013). The most defining symptom associated with fibromyalgia is chronic musculoskeletal pain; however, memory deficits are also common symptoms that heavily impact the well-being and health of people with fibromyalgia (Bair & Krebs, 2020; Kravitz & Katz, 2015). Even though memory and other cognitive deficits may be highly impactful on the functioning and well-being of people with fibromyalgia, there are still many gaps in our understanding (Kravitz & Katz, 2015). Decreases in hippocampal volume have been correlated with worse memory performance in people with multiple sclerosis (Zuppichini & Sandry, 2018) and temporal lobe epilepsy (Reyes et al., 2018). Greater hippocampal activation has also been correlated with worse memory performance in people with mild memory impairment (Yassa et al., 2010), healthy older adults (Leal et al., 2017; Trelle et al., 2020; Yassa et al., 2010, 2011), and healthy younger adults (Leal et al., 2017; Yassa et al., 2011). Further, decreases in hippocampal volume (Leon-Llamas et al., 2021; McCrae et al., 2015) and gray matter (Lutz et al., 2008; Shi et al., 2016) have been identified in people with fibromyalgia. Greater hippocampal activation when anticipating pain (González-Roldán et al., 2016) and imagining pain (Lai et al., 2021), has also been identified in people with fibromyalgia. Yet, the relationship between greater hippocampal activation and memory deficits in people with fibromyalgia remains unclear. This study aimed to better understand the relationship between memory and hippocampal activation in people with

fibromyalgia. We achieved this aim by examining 1) hippocampal activation and memory performance in participants with fibromyalgia compared to healthy adults and 2) the relationship between hippocampal activation and memory performance in people with fibromyalgia.

Memory Deficits in Fibromyalgia

Significant cognitive deficits, termed “fibrofog”, are common symptoms that people with fibromyalgia experience (Bair & Krebs, 2020; Kravitz & Katz, 2015). Fibrofog includes memory deficits, loss of vocabulary, mental slowness, and attention deficits. These deficits impact the functioning and well-being of people with fibromyalgia and are 2.5 times more likely in people with fibromyalgia compared to people with other pain conditions (Kravitz & Katz, 2015). Approximately 76.4%-82.5% of people with fibromyalgia reported cognitive difficulties, 93% of whom reported issues with memory (Kravitz & Katz, 2015).

Past studies have examined deficits in multiple types of memory in people with fibromyalgia. Landrø et al. (1997) tested short-term, long-term episodic, and long-term semantic memory in participants with fibromyalgia and healthy controls; Park et al. (2001) tested working, long-term episodic, and long-term semantic memory in participants with fibromyalgia, age-matched healthy controls, and older healthy controls; Tesio et al. (2015) tested working, short-term, and long-term episodic memory in female participants with fibromyalgia compared to age- and sex-matched healthy controls; and Bell et al. (2018) conducted a meta-analysis of findings from 12 studies testing short-term memory and 11 studies testing long-term memory in participants with Fibromyalgia and age-matched healthy controls. Working memory describes storing and manipulating a small amount of information over a short period (Bell et al., 2018).

For example, mentally repeating a phone number to remember it for a short time. Short-term memory is similar to working memory but does not include manipulating information (Bell et al., 2018). For example, remembering a phone number someone just saw. Finally, long-term memory describes information that has been rehearsed and can be remembered over a long period (Bell et al., 2018). For example, an adult remembering a phone number they learned as a child.

Long-term memory can also be divided into semantic and episodic memory. Semantic memory describes information that is independent of a person's experiences, such as general knowledge (Landrø et al., 1997). For example, remembering the name of the capital of the United States. Episodic memory describes information that is dependent on a person's experiences, such as events. For example, a person remembering their trip to the capital of the United States.

Participants with fibromyalgia performed worse than age-matched healthy controls on working memory tasks (Park et al., 2001; Tesio et al., 2015), short-term memory tasks (Bell et al., 2018), and long-term episodic and semantic memory tasks (Bell et al., 2018; Landrø et al., 1997; Park et al., 2001; Tesio et al., 2015). Additionally, participants with fibromyalgia performed worse than older healthy controls on long-term semantic memory tasks (Park et al., 2001). These results suggest that people with fibromyalgia can have significant deficits in multiple types of memory compared to people without fibromyalgia.

Pattern Separation Deficits in Fibromyalgia

A neurocognitive process involved in multiple types of memory is pattern separation. Pattern separation is the process of separating similar but different stimuli into their distinct representations in the brain (Yassa & Stark, 2011). For example, pattern separation would allow

someone to identify a jacket in a store as different from their own jacket at home. However, if the person has pattern separation deficits, then overgeneralization would occur and the person might perceive the jacket in the store as the jacket they own at home.

Past studies have examined the relationship between pattern separation and memory performance. A study including older adults with mild cognitive impairment, older adults with mild Alzheimer's disease, and healthy older adults, used a spatial pattern separation task to assess discrimination of similar spatial locations. First, participants saw a circle at a specific location on a screen. After a delay, participants were shown two adjacent circles and asked which of the two is in the original location. This assessed their ability to discriminate between the circle in a similar location from the circle in the original location. Older adults with mild Alzheimer's were worse at discriminating the original location from a similar location compared to healthy older adults. Additionally, poorer pattern separation performance was related to greater disease severity and worsening memory (healthy < mild cognitive impairment < mild Alzheimer's) (Parizkova et al., 2020). This demonstrates a link between pattern separation and memory performance.

In addition, studies including younger healthy adults (Yassa et al., 2011), older healthy adults (Yassa et al., 2010, 2011), and participants with mild cognitive impairment (Yassa et al., 2010) tested pattern separation for objects. First, participants saw a series of common household objects. After a delay, they were shown another series of objects containing some of the original images, similar but different images from the original objects, and completely new objects. This assessed their ability to discriminate between similar images and the original images. Older

healthy adults were worse at discriminating the original image from similar images compared to healthy younger adults (Yassa et al., 2011). Similarly, participants with mild cognitive impairment were worse at discriminating the original images from similar images compared to healthy older adults (Yassa et al., 2010). These findings further support the link between pattern separation and memory performance.

Importantly, there is an association between fibromyalgia and pattern separation deficits, especially in the overgeneralization of pain (Meulders et al., 2015, 2017). Participants with fibromyalgia and healthy controls completed a task that involved providing fear ratings to indicate how much they were expecting different movements to cause pain. Participants with fibromyalgia had higher fear ratings for movements associated with no pain than the healthy controls (Meulders et al., 2015, 2017). This suggests that participants with fibromyalgia overgeneralized pain to non-painful movements, which could be indicative of a pattern separation deficit. These prior studies suggest that pattern separation may be related to both memory deficits and pain in people with fibromyalgia. These relationships may have real-world implications. For example, if a person with fibromyalgia experiences pain one day while going on a walk, pattern separation processes could help them recognize that the same pain may not occur while walking on a different day or in a different location. However, if a person with fibromyalgia has pattern separation deficits, then they may overgeneralize the pain from their prior walk to other future walks.

Treatment for Fibromyalgia Symptoms

Treatment for fibromyalgia is limited in the number of treatments available and the efficacy of these treatments (Chinn et al., 2016). Pharmaceutical treatments are the most common for fibromyalgia. Three pharmaceuticals have been approved for use in the United States, but they are not fully effective in treating fibromyalgia. They do not alleviate symptoms in many people with fibromyalgia and may improve but not eliminate symptoms of pain, fatigue, sleep disturbances, depression, and anxiety (Chinn et al., 2016). Non-pharmaceutical treatments, such as aquatic exercise, Tai chi, massages, and acupuncture, have also been observed to help treat fibromyalgia. However, like pharmaceutical treatments, non-pharmaceutical treatments do not alleviate symptoms in many people with fibromyalgia and may improve but do not eliminate symptoms of pain, fatigue, sleep disturbances, depression, and anxiety (Chinn et al., 2016). Importantly, while pharmaceutical and non-pharmaceutical treatments can improve these symptoms in some people, they do not improve cognitive symptoms, like memory deficits (Chinn et al., 2016; Kravitz & Katz, 2015). A better understanding of the neural mechanisms that are associated with these cognitive deficits could lead to the development of more effective treatment options (Chinn et al., 2016).

The Role of the Hippocampus in Memory

The hippocampus and its connections to surrounding regions have been established as critical for many types of memory, especially long-term memory, through verbal responses, functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) imaging in humans (Aggleton, 2012; Cohen et al., 1999; Eichenbaum, 2004; Renoult et al., 2019;

Squire et al., 2004; Stark & Squire, 2000; Yonelinas et al., 2024). Verbal responses have been used to measure memory performance, while fMRI and PET images have been used to illustrate changes in hippocampus function (Glover, 2011; Lameka et al., 2016). In previous studies, participants completed long-term memory tasks during fMRI and PET scanning to examine the hippocampus during long-term memory recall. During scanning, participants were shown images of objects, places, or words and then asked to recall what was shown after a delay. When information was correctly remembered after the delay, participants had greater hippocampal activation (Aggleton, 2012; Cohen et al., 1999; Eichenbaum, 2004; Renoult et al., 2019; Squire et al., 2004; Stark & Squire, 2000; Yonelinas et al., 2024). These findings suggest that greater hippocampal activation is associated with greater long-term memory performance, illustrating that the hippocampus plays an important role in long-term memory.

Further, chemical damage to the hippocampus has supported the findings mentioned above. In mice, inhibition of the hippocampus with lidocaine resulted in deficits in spatial navigation, a form of long-term memory. Unlike humans, who can indicate what they remember verbally, long-term memory was measured in the mice based on their behavioral responses. First, the mouse learned which arm out of two held food. After a delay, memory was tested by assessing whether the mouse walked to the arm that had the food. The mice that had their hippocampi temporarily inhibited walked to the arm that had food less compared to mice that did not have hippocampal inhibition (Mingaud et al., 2007). This suggests that the hippocampus is important for successful long-term memory performance.

Physical damage to the hippocampus in humans has also supported the key role that the hippocampus plays in memory. Participants with amnesia from bilateral inflammation and swelling of hippocampal tissue and healthy controls completed a long-term memory assessment. Participants were given verbal prompts related to events in their lives verified by family or peers and then asked to recall the event related to the prompt. Details recalled by the participants were verified by the participants' families and peers. The authors also rated each recalled detail as episodic or semantic. Participants with amnesia recalled fewer episodic details than healthy controls and recalled similar levels of semantic details compared to healthy controls (Miller et al., 2020). These findings suggest that damage to the hippocampus is associated with worse episodic memory but not semantic memory. These findings support the conclusion that the hippocampus plays a critical role in memory; however, it also suggests that the hippocampus may play a more critical role in some types of memory than others.

The Role of the Hippocampus in Pattern Separation

While it has been established that the hippocampus plays a role in memory, more recent research has focused on the role the hippocampus has in specific neurological processes, such as pattern separation. Acquired bilateral hippocampal damage from physical trauma was associated with pattern separation deficits. Participants were shown a series of images and were asked to respond to each image with "pleasant" or "unpleasant". After a delay, participants were shown a new series of images consisting of original images, similar images, and new images. They were asked to respond if they recognized each image as being an original image, a similar image, or a new image. Assessing if participants could discriminate between original images and similar

images determined if pattern separation occurred. Participants with bilateral hippocampal damage were worse at discriminating between original and similar images and responded with “original” to the similar images more often than the healthy controls (Kirwan et al., 2012). This finding suggests that damage to the hippocampus is associated with worse pattern separation performance.

The Relationship Between Hippocampal Structure and Pattern Separation

Decreased hippocampal volume has been linked to worse pattern separation performance (Reyes et al., 2018; Zuppichini & Sandry, 2018). While this relationship has not been observed in people with fibromyalgia, links between hippocampal volume and pattern separation deficits have been observed in other clinical populations. In participants with multiple sclerosis, a neurological disorder, responses to a task measuring pattern separation illustrated a deficit in pattern separation compared to healthy controls. Additionally, a relationship between decreased hippocampal volume and worse pattern separation performance was observed in participants with multiple sclerosis (Zuppichini & Sandry, 2018).

Further, the link between decreased hippocampal volume and worse pattern separation performance was also observed in people with temporal lobe epilepsy, a seizure disorder that can be associated with abnormal hippocampal structure. Participant responses to a recognition task illustrated deficits in pattern separation compared to healthy controls. Participant responses and MRI images also illustrated a correlation between decreased hippocampal volume and worse pattern separation performance (Reyes et al., 2018). These studies suggest that a lower number of neurons in the hippocampus is disadvantageous for pattern separation, while a greater number

of neurons in the hippocampus is beneficial for pattern separation. However, more research is needed to examine whether these findings are also observed in people with fibromyalgia.

The Relationship Between Hippocampal Function and Pattern Separation

Prior studies have not examined links between pattern separation performance and hippocampal function in participants with fibromyalgia, but several studies have examined this relationship in older adults (Leal et al., 2017; Trelle et al., 2020; Yassa et al., 2010, 2011), younger adults (Leal et al., 2017; Yassa et al., 2011), and in participants with mild memory impairments (Yassa et al., 2010). All of these studies reported a significant correlation between greater hippocampal activation and worse pattern separation performance (Leal et al., 2017; Trelle et al., 2020; Yassa et al., 2010, 2011). These findings support a relationship between greater hippocampal activation and greater pattern separation deficits. One interpretation of these findings is that, even though the hippocampus is working harder, hyperactivity in the hippocampus is not benefiting pattern separation performance (Leal et al., 2017; Yassa et al., 2010, 2011). Future studies including participants with fibromyalgia are needed to examine whether this conclusion is also observed in people with fibromyalgia.

The findings on the relationship between decreased hippocampal volume and pattern separation deficits and the relationship between increased hippocampal activation and pattern separation deficits also suggest that there may be a relationship between decreased hippocampal volume and increased hippocampal activation; although, this relationship needs further examination. While no literature currently examines why this relationship exists, one theory could be that in reaction to the loss of hippocampal volume and gray matter, the hippocampus

works harder during pattern separation in an attempt to compensate for the lost neurons.

However, the hippocampus cannot fully compensate and the hyperactivation becomes dysfunctional for pattern separation performance (Yassa et al., 2011). A second theory could be that the loss of hippocampal volume and gray matter disrupts neurological networks needed for pattern separation. Hyperactivity in the hippocampus could then be a marker of this neurological disruption rather than a reaction to it (Leal et al., 2017; Yassa et al., 2010).

The Relationship between Fibromyalgia and Hippocampal Structure

While prior studies have not specifically examined hippocampal structure associated with pattern separation performance in people with fibromyalgia, they have illustrated that hippocampal structure is different in people with fibromyalgia compared to healthy individuals. Magnetic resonance imaging (MRI) of the hippocampus illustrated that female participants with fibromyalgia had a bilateral decrease in hippocampal volume compared to female healthy controls (Leon-Llamas et al., 2021; McCrae et al., 2015). Hippocampal volume can also be divided into gray matter volume and white matter volume. Gray matter consists of neuronal cell bodies that contain neuronal DNA. Without DNA, a neuron loses its ability to process and send information and becomes dysfunctional (Mercadante & Tadi, 2024). MRI brain scans have illustrated that participants with fibromyalgia had a decrease in gray matter volume in the hippocampus and surrounding brain regions compared to healthy controls (Lutz et al., 2008; Shi et al., 2016). A decrease in gray matter in the hippocampus suggests that the loss of neuronal cell bodies and DNA leads to a decrease in functional hippocampal neurons. Thus, people with fibromyalgia have less functional hippocampal neurons than healthy individuals.

The Relationship between Fibromyalgia and Hippocampal Function

There are minimal studies on hippocampal function in people with fibromyalgia, but they do not examine hippocampal activation during pattern separation. One study examined hippocampal function when people with fibromyalgia anticipated pain. Female participants with fibromyalgia and female healthy controls completed a pain expectation task during fMRI scanning. During the task, participants were given feedback on whether they would feel low or high pain, followed by a delay before painful heat stimulation was applied to one of their hands. When anticipating the pain, participants with fibromyalgia had greater hippocampal activation compared to the healthy controls (González-Roldán et al., 2016). This suggests that people with fibromyalgia have greater hippocampal function when expecting pain.

Another study examined brain activation in participants with fibromyalgia, participants with chronic lower back pain, and healthy controls during the presentation of painful or non-painful postures. Participants viewed a series of painful and non-painful postures and were asked to imagine themselves in the different postures while an electroencephalogram (EEG) with low-resolution electromagnetic tomography was used to estimate regions of activation within the brain. Participants with fibromyalgia had greater hippocampal activation during the presentation of painful postures compared to the presentation of non-painful postures. Additionally, participants with fibromyalgia had different brain activity in response to painful and non-painful postures compared to participants with chronic back pain and healthy controls. Participants with chronic back pain and healthy controls had lower hippocampal activation during the presentation of painful postures compared to the presentation of non-painful postures (Lai et al., 2021). These

findings suggest that people with fibromyalgia have greater hippocampal activation when imagining pain compared to when they are not imagining pain. These findings also suggest that people without fibromyalgia do not have greater hippocampal activation when imagining pain compared to when they are not imagining pain. The findings from these studies may have relevance to pattern separation in fibromyalgia, as a person with fibromyalgia may overgeneralize and expect or imagine pain with non-painful stimuli (González-Roldán et al., 2016; Lai et al., 2021). However, further research specifically measuring hippocampal function in people with fibromyalgia during pattern separation is needed.

The Present Study

Previous studies provide important information about relationships between hippocampal structure and function and pattern separation deficits (Leal et al., 2017; Reyes et al., 2018; Trelle et al., 2020; Yassa et al., 2010, 2011; Zuppichini & Sandry, 2018). However, these studies have not examined these relationships in participants with fibromyalgia. As a result, these relationships in people with fibromyalgia are unclear. Importantly, studies including participants with fibromyalgia have illustrated decreases in hippocampal volume and greater hippocampal activation when anticipating and imagining pain (González-Roldán et al., 2016; Lai et al., 2021; Leon-Llamas et al., 2021; Lutz et al., 2008; McCrae et al., 2015; Shi et al., 2016). These findings suggest that the relationship between the hippocampus and pattern separation is important to further study, to develop more effective treatments for the memory deficits commonly reported in fibromyalgia. Additional studies are needed to examine hippocampal activation during pattern

separation in people with fibromyalgia compared to healthy individuals, as well as relationships between hippocampal activation and pattern separation performance in people with fibromyalgia.

To fill these gaps, the present study focused on three research questions. First, we examined whether there was a difference in pattern separation performance between participants with fibromyalgia and healthy controls. We hypothesized that participants with fibromyalgia would have worse pattern separation performance compared to healthy controls. Second, we examined whether there was a difference in hippocampal activation during pattern separation between participants with fibromyalgia and healthy controls. We hypothesized that participants with fibromyalgia had greater hippocampal activation during pattern separation compared to healthy controls. Finally, we examined whether hippocampal activation correlated with pattern separation performance in participants with fibromyalgia. We hypothesized that greater hippocampal activity was correlated with worse pattern separation performance in participants with fibromyalgia.

Methods

Participants

The participants included in this study were recruited in the context of a larger study examining neural correlates of learning and memory in people with post-traumatic stress disorder and fibromyalgia. The study recruited right-handed adults ranging from 18-45 years old from the University of Michigan medical and academic campuses and the larger Ann Arbor community. Recruitment methods included advertisement through the University of Michigan's U-M Health Research recruitment website, social media, and flyers posted in the Ann Arbor community and

university buildings. The present study is a secondary analysis that used a subsample of the participants. The subsample included 26 participants: 10 participants with fibromyalgia and 16 healthy controls. The participants ranged in age from 18-44 years ($M = 29.04$). Twenty-two participants identified as women (84.62%) and four identified as men (15.38%). Three participants identified as Asian (11.54%); one as Hispanic and White (3.85%); and 22 as Non-Hispanic and White (84.61%). Two participants with fibromyalgia and four healthy controls did not complete the Mnemonic Similarity Task (MST) and were excluded from analyses. One participant with fibromyalgia was excluded for data preprocessing errors. Two participants with fibromyalgia and one healthy control had technical errors in data collection and were excluded from the analyses. Our final sample consisted of five participants with fibromyalgia and 11 healthy controls.

Participants in the fibromyalgia group had a documented, pre-existing diagnosis of fibromyalgia. The inclusion criteria for healthy controls included being free of any chronic pain, mental health conditions, and substance use disorders. The exclusion criteria for all participants included having a significant medical or neurological condition (stroke, seizures, multiple sclerosis); having a primary mood disorder or suicidality; using psychotropic medication that impacts cognitive processes; having a life history of schizophrenia, bipolar disorder, cognitive impairment, or pervasive developmental disorder; being unwilling or unable to provide informed consent; and having a contraindication for an MRI scan (e.g., a pacemaker or other metal in/on the body).

Procedures and Tasks

Written informed consent was obtained from each participant prior to beginning data collection. All study procedures were approved by the University of Michigan's Institutional Review Board (IRBMED). The study included multiple visits that were conducted over the course of three days. During the first visit, participants completed an evaluation to determine eligibility and assess a variety of mental and physical conditions. During the second visit, participants completed learning and memory tasks outside of fMRI scanning. Then, during the third visit (the day after the second visit), participants completed learning and memory tasks during fMRI scanning. The present study is specifically focused on behavioral and fMRI data collected from the MST during the third study visit.

Mnemonic Similarity Task

This task has been used previously to test pattern separation performance and associated activation in the hippocampus (Stark et al., 2019). The MST is made up of two phases: an encoding phase and a test phase. During the encoding phase, 128 images of common objects were shown to the participants. Participants were asked to identify if the object would be found indoors or outdoors. During the test phase, participants were shown 64 of the same images previously shown (old), 64 images that looked similar to, but were different from the previously shown images (similar), and 64 images never shown that were completely different images (new). Participants were instructed to say if the image shown is "old," "similar," or "new." Correct "old" responses would mean that the participant recognized the image as a previously shown image, correct "similar" responses would mean that the participant recognized the image

is similar to a previously shown image, and correct “new” responses would mean that the participant recognized the image as different to the previously shown images.

When participants respond “similar” to a similar image, their response indicates pattern separation occurred because they could identify and differentiate that the current image was similar, but not the same as the original image they retrieved from their memory. On the other hand, when participants respond “old” to a similar image, their response indicates pattern separation did not occur and they could not differentiate that the current image was not the same as the original image they retrieved from their memory. Rather, they overgeneralized the previously shown image in their memory to the current image. A “similar” response to a new image would indicate that the participant may have a bias towards responding with “similar” to all images.

Consistent with scoring recommendations on the MST, pattern separation performance was scored by subtracting the proportion of “similar” responses for new images from the proportion of “similar” responses for similar images (Stark et al., 2019). This calculation corrects for potential bias that a participant may have to respond with “similar” to all images. Greater scores indicate better pattern separation performance.

Hippocampal Activation

High-resolution fMRI scans designed to capture function in the hippocampus were collected on a GE 3-T Discovery MR750 Series MRI. T1-weighted anatomic images were collected with a 3D MPRAGE sequence (FOV = 256 x 256 mm, slice thickness = 1 mm, 0 mm gap). Functional scans consisted of gradient echo blood oxygen level-dependent (BOLD) scans

collected during the MST with the following parameters: TR/TE = 2000/28 ms, flip angle = 90, FOV = 192 x 192 mm, slice thickness = 1.2 mm.

Data Processing

Before preprocessing, we removed non-brain tissue from the MRI images. fMRI scans were then preprocessed using a custom script for Statistical Parametric Mapping (SPM12) software in MATLAB (R2021a). Preprocessing included slice-time correction, realignment, coregistration to structural images, normalization to the Montreal Neurological Institute (MNI) template brain, and smoothing with a 2 mm kernel. Slice-time correction corrected the slices to look like they were taken simultaneously rather than one by one. Realignment aligned all the slices of one scan together to produce an image of the whole brain. Coregistration to structural images was completed to align a participant's low-resolution functional scan that indicates patterns of activation with their high-resolution structural scan that allows for localization of specific brain regions. Normalization to the MNI corrected for participant-specific brain differences (e.g., differences in brain size and shape between participants) and resulted in standardized scans with the same dimensions. Smoothing with a 2 mm kernel averaged the activation at one coordinate with the activation at coordinates surrounding it in a 2 mm radius throughout the scan to remove noise from the signal.

After preprocessing, coregistration and normalization were manually evaluated. Manual evaluation involved the researcher visually confirming that the hippocampus and the back of the brain in the participant's functional scan were aligned to the hippocampus and the back of the brain in the participant's structural scan and the MNI template brain. If a participant's functional

scan did not have the hippocampus and the back of the brain aligned to the structural scan and the MNI template brain, they were excluded from the analyses. Additionally, participant movement in the scanner on six dimensions (x, y, z, pitch, roll, yaw) was evaluated. If a participant's scan included more than 3 mm of maximum movement or more than 0.7 mm of average movement, the scan was excluded from the analysis. One participant with fibromyalgia was excluded from the analyses due to both runs failing the manual evaluation for normalization. No participants were excluded for excessive motion. Two participants with fibromyalgia and one healthy control were excluded from the analyses for having technical errors during data collection in both runs. One healthy control had one run excluded from analyses due to technical errors during data collection, but data from their other run was included.

Statistical Analysis

To test the hypothesis that participants with fibromyalgia had worse pattern separation performance compared to healthy controls, a two-sample t-test was used. The independent variable was whether the participant had fibromyalgia or not. The dependent variable was the pattern separation score. To test the hypothesis that participants with fibromyalgia had greater hippocampal activation during pattern separation compared to healthy controls, a two-sample t-test was used. The independent variable was whether the participant had fibromyalgia or not. The dependent variable was hippocampal activation during trials when similar images were shown. To test the hypothesis that greater hippocampal activity during pattern separation was correlated with worse pattern separation performance in participants with fibromyalgia, we included pattern separation score as a predictor of hippocampal activation using correlation

analysis in the participants with fibromyalgia. Due to our small sample size, the significance threshold for all fMRI analyses was set to a liberal cutoff of $p < 0.01$, uncorrected. Thus, all results reporting hippocampal activation should be treated as preliminary.

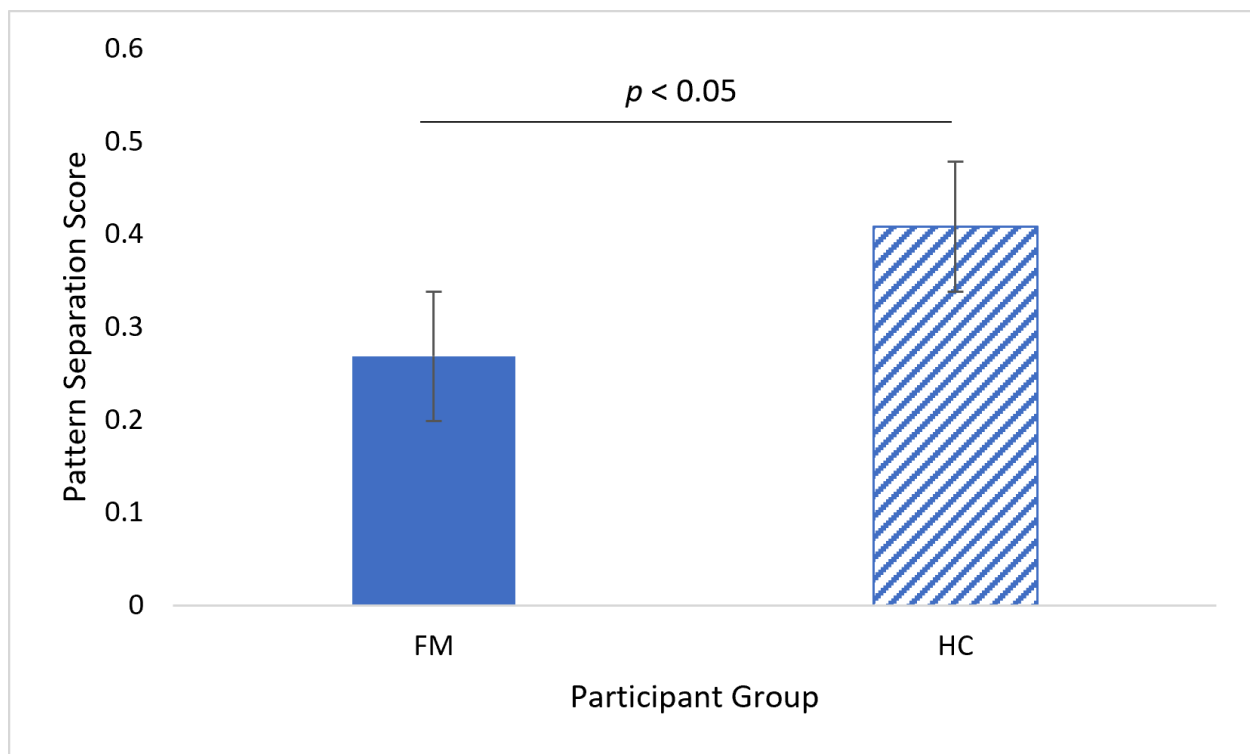
Results

Pattern Separation Performance

To assess pattern separation performance in participants with fibromyalgia compared to healthy controls, we compared mean pattern separation scores between groups using a two-sample t-test. We found that participants with fibromyalgia performed significantly worse during pattern separation ($M = 0.27$) than healthy controls ($M = 0.41$; $p < 0.05$; $t = 1.77$; Figure 1).

Figure 1

Lower Mean Pattern Separation Performance in Participants with Fibromyalgia (FM) Compared to Healthy Controls (HC)



Note. Error bars represent standard error.

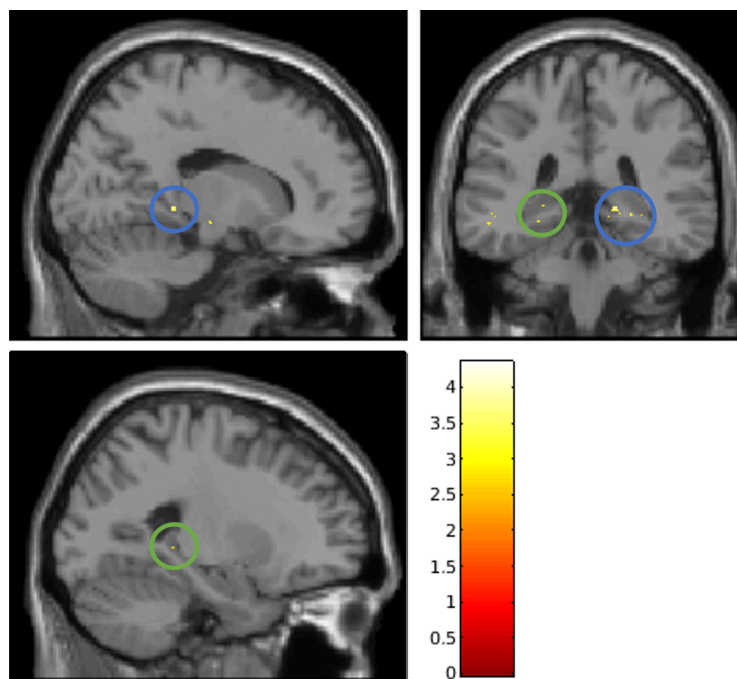
Hippocampal Activation During Pattern Separation

To assess hippocampal activation during pattern separation in participants with fibromyalgia compared to healthy controls, we used a two-sample t-test to compare groups on hippocampal activation during trials when similar images were shown. We found greater left hippocampal activation to similar images in participants with fibromyalgia compared to healthy controls (coordinates $[x, y, z] = -23, -37, 0$; $p < 0.01$, uncorrected; $T = 2.65$; and coordinates $[x, y,$

$z] = -15, -36, 2; p < 0.01$, uncorrected; $T = 3.42$; Figure 2). We also found greater right hippocampal activation to similar images in participants with fibromyalgia compared to healthy controls (coordinates $[x, y, z] = 25, -37, -5; p < 0.01$, uncorrected; $T = 3.07$; and coordinates $[x, y, z] = 17, -37, -1; p < 0.01$ uncorrected; $T = 3.75$; Figure 2).

Figure 2

Greater Bilateral Hippocampal Activation in Participants with Fibromyalgia Compared to Healthy Controls



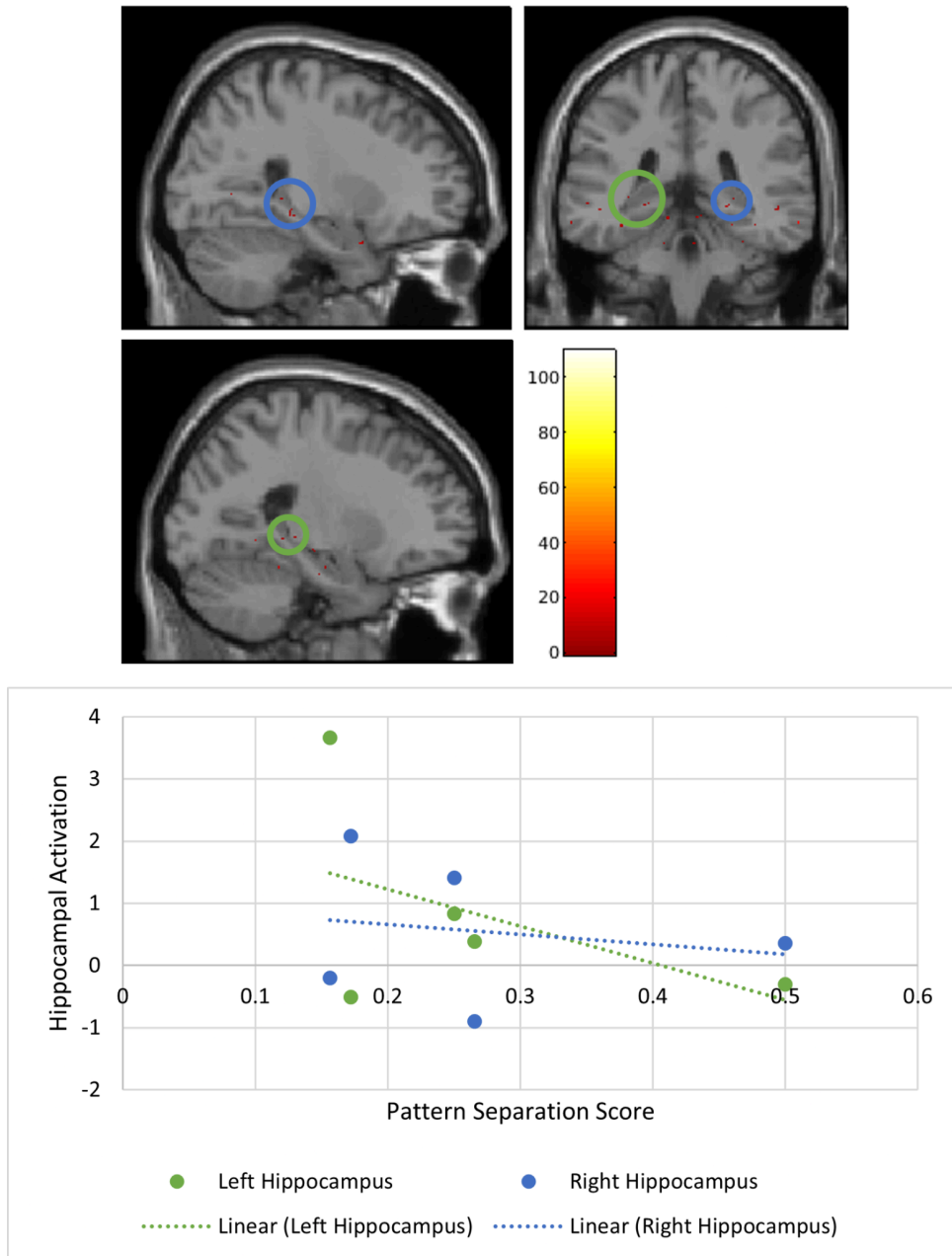
Note. $p < 0.01$, uncorrected.

Relationship Between Hippocampal Activation and Pattern Separation Performance in Fibromyalgia

To assess the relationship between hippocampal activation and pattern separation performance in fibromyalgia, we used a correlation analysis to examine the relationship between hippocampal activation during trials when similar images were shown and pattern separation scores in participants with fibromyalgia. We found greater left hippocampal activation to similar images was correlated with lower pattern separation scores in participants with fibromyalgia (coordinates $[x, y, z] = -22, -38, -3$; $p < 0.01$, uncorrected; $T = 6.67$; Figure 3). We also found greater right hippocampal activation to similar images was correlated with lower pattern separation scores in participants with fibromyalgia (coordinates $[x, y, z] = 23, -36, -3$; $p < 0.01$, uncorrected; $T = 10.68$; Figure 3).

Figure 3

Greater Bilateral Hippocampal Activation Correlated with Worse Pattern Separation Performance in Participants with Fibromyalgia



Note. $p < 0.01$, uncorrected.

Discussion

Pattern Separation Deficits

This study aimed to answer three research questions. The first was whether there would be a difference in pattern separation performance between participants with fibromyalgia and healthy controls. We hypothesized that participants with fibromyalgia would have worse pattern separation performance compared to healthy controls, and this hypothesis was supported. We found that people with fibromyalgia have pattern separation deficits compared to healthy controls. This conclusion is consistent with previous findings on pattern separation deficits in people with fibromyalgia (Meulders et al., 2015, 2017). Like previous studies, these findings may suggest that people with fibromyalgia overgeneralize, not differentiating previously learned stimuli from similar stimuli, in contexts where generalization should not occur.

Hippocampal Activation

The second question was whether there would be a difference in hippocampal activation during pattern separation between participants with fibromyalgia and healthy controls. We hypothesized that participants with fibromyalgia would have greater hippocampal activation during pattern separation compared to healthy controls. The preliminary finding that greater bilateral hippocampal activation during the presentation of similar images in participants with fibromyalgia compared to healthy controls supports our hypothesis. Further, these findings suggest that people with fibromyalgia have a hyperactive hippocampus during pattern separation compared to healthy individuals. This could suggest that the hippocampus is working harder during pattern separation in people with fibromyalgia compared to healthy individuals. This

conclusion is somewhat consistent with previous findings that also reported that the hippocampus was more active (potentially working harder) in people with fibromyalgia during anticipation and imagining pain (González-Roldán et al., 2016; Lai et al., 2021). While the current study did not examine pain-related processes, our findings expand on the previous work to suggest that the hippocampus is more active in people with fibromyalgia during many different contexts and not just when anticipating or imagining pain.

However, our conclusion is inconsistent with other findings that illustrated participants with fibromyalgia having lower hippocampal activation when learning and paying attention to visual images compared to healthy controls (Martinsen et al., 2014). This observation conflicts with our findings and suggests that the hippocampus was less active (potentially working less) in people with fibromyalgia compared to healthy individuals. This discrepancy in findings may suggest that whether the hippocampus is more or less active in fibromyalgia depends on what cognitive function is occurring. For example, memory function may be associated with the hippocampus working harder in people with fibromyalgia compared to healthy individuals, while attentional function may be associated with the hippocampus working less in people with fibromyalgia compared to healthy individuals. Future research is needed to better understand how different cognitive processes are associated with hippocampus function in people with fibromyalgia compared to healthy individuals.

Relationships between Pattern Separation Deficits and Hippocampal Activation

Finally, the third question was whether there was a relationship between pattern separation and hippocampal activation in participants with fibromyalgia. We hypothesized that

worse pattern separation performance would be associated with greater hippocampal activation in participants with fibromyalgia. The preliminary finding that greater hippocampal activation was associated with worse pattern separation performance in participants with fibromyalgia supports our hypothesis. This suggests that the hippocampus working harder is not associated with improved pattern separation performance in people with fibromyalgia. This is consistent with prior studies that also reported a relationship between greater hippocampal activation and worse pattern separation performance (Leal et al., 2017; Trelle et al., 2020; Yassa et al., 2010, 2011). These studies also conclude that more activation in the hippocampus, suggestive of greater effort, was associated with greater pattern separation deficits rather than improved pattern separation abilities.

While these studies are consistent with our findings, many prior studies have observed the opposite relationship between hippocampal activation and memory performance. Participants with the gene KIBRA, a gene associated with better memory abilities, had greater hippocampal activation (Kauppi et al., 2011; Witte et al., 2016), greater short-term memory performance (Witte et al., 2016), and greater long-term memory performance (Kauppi et al., 2011; Witte et al., 2016) compared to healthy controls. Male participants with stress had lower hippocampal activation and worse episodic memory performance than male healthy controls (Gagnon et al., 2019). Participants with mild cognitive impairment had lower hippocampal activation and worse associative memory performance, a specific type of episodic memory performance, compared to older healthy controls (Petrella et al., 2006). These findings suggest that greater hippocampal

activation is beneficial for memory performance. These studies conclude that when the hippocampus works harder, it works better and memory performance increases.

These inconsistencies in the relationship between memory performance and hippocampal activation suggest that hippocampal activation may be related to performance differently for different aspects of memory. Thus, some aspects of memory may benefit from the hippocampus working harder, while other aspects of memory, like pattern separation, may not benefit from the hippocampus working harder. Future research is needed to examine how greater hippocampal activation relates to memory performance.

Limitations and Future Directions

A major limitation is the size and make-up of our sample. 16 participants were included in analyses after exclusions, five of whom were participants with fibromyalgia. Additionally, the sample primarily consisted of women and White individuals, with 84.62% of the participants identifying as women and 84.61% of the participants identifying as non-Hispanic and White. The small sample size and lack of diversity results in inconsistencies between the study's sample and the general population, which can decrease the findings' reliability and generalizability. Additionally, the small sample size and liberal threshold used for determining significance in the neuroimaging data prevent us from drawing strong conclusions from our results. As fibromyalgia is more common in females than males, sex may also be a confounding variable that could relate to hippocampal activation and pattern separation in fibromyalgia (Bair & Krebs, 2020). Future research using larger and more diverse samples is needed.

In addition, this study did not examine the mechanisms causing greater hippocampal activation and worse pattern separation performance in people with fibromyalgia. While these findings suggest a relationship between fibromyalgia, hippocampal activation, and pattern separation, causal conclusions cannot be established. Future research on the mechanisms underlying this relationship is necessary to best understand the cause of pattern separation deficits in people with fibromyalgia. A better understanding of these mechanisms can aid in advancing fibromyalgia treatments, especially in addressing the cognitive symptoms associated with fibromyalgia (Chinn et al., 2016).

Conclusion

In summary, this study aimed to examine differences in pattern separation and hippocampal activation between participants with fibromyalgia and healthy controls, as well as the relationship between pattern separation and hippocampal activation in participants with fibromyalgia. The findings suggest that people with fibromyalgia have pattern separation deficits and hyperactivation of the hippocampus and that these pattern separation deficits are associated with hyperactivation of the hippocampus. To conclude, this study illustrates the importance of hippocampal activation in relation to pattern separation in people with fibromyalgia and supports the need for further research on this subject. Expanding the understanding of neuronal correlates and mechanisms associated with pattern separation deficits in people with fibromyalgia may be fundamental in producing better treatments that can target cognitive deficits.

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