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Mood and Memory: An Association Between Pattern Separation and Depression

Don J. Shelton

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

C. Brock Kirwan, Chair
Ramona O. Hopkins
Shawn D. Gale

Department of Psychology

Brigham Young University

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ABSTRACT

Mood and Memory: An Association Between
Pattern Separation and Depression

Don J. Shelton
Department of Psychology, BYU
Master of Science

Depression is associated with reduced declarative memory performance and decreased hippocampal volume. Depression has also been associated with decreased levels of adult neurogenesis in the dentate gyrus. Computational models propose that neurogenesis is critical for the computational process of pattern separation, whereby distinct memory representations are created for very similar stimuli and events. It has been proposed that depression negatively impacts pattern separation abilities; however, a link between depression and performance in pattern separation memory tasks has yet to be investigated. Accordingly, we designed a study to investigate the relationship between pattern separation performance and the severity of depression symptoms. Participants completed a recognition memory test with high pattern separation demands as well as a set of questionnaires to gauge their level of depression. We found a negative relationship between depression scores and pattern separation scores in support of the theory that depression is negatively related to pattern separation performance.

Keywords: depression, pattern separation, neurogenesis, mood disorders

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Mood and Memory: An Association between Pattern Separation and Depression

Memory gives our lives meaning. Without it, we would be trapped in a repetitive "now," unable to learn or progress. We would have no recollection of people that are important to us, no anticipation of future events, and no sense of identity based on our past experiences. While a functioning memory system saves most of the population from such ailments, there are many people who suffer from some degree of memory loss for a variety of reasons. In particular, memory impairment may occur in depressed patients (Burt, Zembar, & Niederehe, 1995), compounding an already devastating mental disorder. Some researchers estimate that within 20 years, depression will be the leading cause of illness in western nations, accounting for 5.7% of total disability adjusted life years, and the second leading cause of illness worldwide (Mathers & Loncar, 2006). In light of these projections, it is increasingly important to understand depression and its effects on memory.

Memory is subdivided into several component systems, each of which is supported by specific brain regions. Learning and memory performed without conscious awareness of previous experience is called non-declarative or implicit memory. Conversely, memory for specific facts and events is called declarative or explicit memory. Medial temporal lobe structures, including the hippocampus, are critical for declarative memory (Scoville & Milner, 1957; Squire & Zola-Morgan, 1991). Within these structures, mood disorders like depression have physiological effects such as glutamate abnormalities (Beneyto, Kristiansen, Oni-Orisan, McCullumsmith, & Meador-Woodruff, 2007) and volumetric changes (Bremner et al., 2000). Behavior studies demonstrate that declarative memory is impaired in depression, whereas non-declarative memory is not impaired (Bazin, Perruchet, De Bonis, & Féline, 1994; Burt et al.,

1995; Ellwart, Rinck, & Becker, 2003; Zakzanis, Leach, & Kaplan, 1998). Though the association between depression and declarative memory impairments are well documented, the mechanisms behind this association are not yet well understood. We hypothesize that depression may be associated with the inhibition of memory processes specific to the hippocampus and therefore lead to this memory impairment. This study will examine the link between depression and memory, physiological reasons for impaired memory in depression, and describe memory theories that may explain the observed memory impairment.

Declarative Memory is Reduced in Depression

Studies have demonstrated declarative memory impairments for individuals with depression. Bazin and colleagues (1994) tested memory in depressed patients using a cued-recall test and a word-stem completion task. Depressed patients had declarative memory impairments, but no impairment in non-declarative memory compared to healthy controls. In a similar study, Ellwart et al. (2003) tested declarative memory in depressed patients using a free-recall test and an anagram task and found impaired declarative memory in the depressed group, but no impairments in non-declarative memory. MacQueen and colleagues (2002) found the frequency of past depressive episodes predicted memory performance but current mood was not indicative of memory performance. A meta-analysis that synthesized data from 147 studies on declarative memory in clinically depressed and non-depressed patients found depression was associated with declarative memory impairments (Burt et al., 1995). In a separate meta-analysis of studies involving 726 patients with depression and 795 healthy controls, depression had the largest adverse effect on episodic memory, which is memory for life events, and a significant but less substantial effect on semantic memory, which is memory for facts (Zakzanis et al., 1998). Spatial memory is also affected in individuals with depression. Patients with depression performed

worse on navigation in a virtual town compared to healthy comparison subjects (Gould et al., 2007). Interestingly, both declarative memory and depressed mood improve with the administration of selective serotonin reuptake inhibitors (SSRIs) (Levkovitz, Caftori, Avital, & Richter-Levin, 2002). These studies demonstrate a clear link between depression and impaired declarative memory.

Pattern Separation

In his landmark research, Marr (1971) developed a computational model of the hippocampus that has been instrumental to the current understanding of declarative memory. Marr predicted that recurring axons within the hippocampal subregion CA3 would be heavily involved in forming declarative memory representations. Other computational models have built on Marr's idea by suggesting that declarative memory relies on the ability to represent similar experiences or events as separate, non-overlapping representations using a process called pattern separation (Marr, 1971; Norman & O'Reilly, 2003; Rolls, 1996; Treves & Rolls, 1992; Treves, Tashiro, Witter, & Moser, 2008).

Pattern separation in memory allows individuals to form distinct, non-overlapping representations of similar episodes. For instance, an individual might repeatedly park in the same parking lot but in different stalls each day. Pattern separation would allow the individual to distinguish each day's unique parking location from the collective memory of every other parking location, so the individual is able to find their car at the end of the day without walking to a previous, though very similar, location. In order to be effective, pattern separation must sufficiently discriminate, but not be overactive. Psychological disorders may be related to a tendency for overactive or insufficient pattern separation. Overactive pattern separation may result in excessive attention to details (for example, autism, or obsessive compulsive disorder),

whereas insufficient pattern separation may results in excessive generalization (e.g., anxiety, depression, post-traumatic stress disorder) (Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Lissek, 2012; Sahay & Hen, 2007). However to date the relationship between pattern separation and depression has not be examined.

Current models of pattern separation stress the role of the dentate gyrus (a hippocampal subregion) in separating inputs and encoding different memories in the CA3 (Rolls, 1996; Treves et al., 2008). To test these models, Gilbert, Kesner, and DeCoteau (1998) developed a behavioral test that measured the ability of rats to discriminate spatial distance between two similar objects. When compared to healthy controls, rats with hippocampal lesions were unable to judge between two objects placed closely together. However, as the spatial distance between the two objects increased, the hippocampal lesioned rats' performance improved. In a follow up study, the same research group compared the effects of lesions on two different regions of the dorsal hippocampus: the dentate gyrus and CA1. Rats with dentate gyrus lesions had deficits on spatial pattern separation tasks but not temporal separation tasks. In contrast, rats with CA1 lesions had deficits on temporal separation but not spatial separation tasks (Gilbert, Kesner, & Lee, 2001).

A more focused look at the encoding and retrieval pathways of the hippocampus shows that the perforant pathway allows direct communication from the entorhinal cortex to the CA3. Alternatively, the entorhinal cortex can communicate with the CA3 through the dentate gyrus and its mossy fiber connections. Lee and Kesner (2004) were able to discriminate memory functionality of the CA3 by examining its input pathways from the entorhinal cortex. Lesions in the dentate gyrus pathway resulted in deficits to spatial memory encoding, but did not compromise spatial memory retrieval, whereas lesions in the direct perforant pathway connections resulted in deficits in the retrieval but not the encoding of spatial memory.

Human studies using behavioral measures and functional magnetic resonance imaging (fMRI) have been used to assess pattern separation. Kirwan et al. (2012) recently demonstrated that patients with damage limited to the hippocampus were differentially impaired on a pattern separation task while recognition memory was relatively unimpaired. Functional MRI studies find that the hippocampus is involved when pattern separation demands are high (e.g., Kirwan and Stark, 2007) and that the specific pattern of hippocampal activity depends on the current task demands (Motley & Kirwan, 2012). Using a continuous recognition memory task, Bakker and colleagues (2008) found the dentate gyrus and CA3 are critically involved in the process of pattern separation.

Studies of pattern separation in healthy older adults find pattern separation deficits when compared with younger adults (e.g., Toner et al., 2009). Pattern seperation deficits were also observed in healthy older adults (Yassa and colleagues (2011). Additionally, fMRI activity in the CA3 was increased in younger adults relative to older adults in a pattern separation task (Yassa et al., 2011). These deficits are theorized to be due to a shift in the elderly brain from pattern separation to other memory processes. Similarly, in an experiment based on a spatial pattern separation paradigm used previously with rats, Holden, Hoebel, Loftis, and Gilbert (2012) human participants' overall performance mirrored performance of the rodents on a human version of the task (Holden, Hoebel, Loftis, and Gilbert (2012). Furthermore, older adults were impaired for memory for target-lure distances, relative to younger adults, consistent with decreased pattern separation ability in aging.

These studies suggest that pattern separation is necessary for encoding declarative memories and the hippocampus is especially well suited to perform this process. There is good

reason to suggest that the process of pattern separation may be impaired in the case of depression when one considers the physiological changes in the hippocampus associated with depression.

Changes of Hippocampal Physiology with Depression

Studies demonstrate that hippocampal volume is smaller in patients with depression than in non-depressed controls (Bremner et al., 2000; Campbell, Marriott, Nahmias, & MacQueen, 2004; Videbech & Ravnkilde, 2004). Chronically depressed patients have reduced hippocampal volume, but individuals experiencing their first depressive episode show no such volume reduction (MacQueen et al., 2003), suggesting that hippocampal volume is also related to total time depressed and length of untreated depression. The reduction in hippocampal volumes is attributed to a number of factors including dendritic retraction, neuronal death, and suppression of adult neurogenesis. Yet to date the reason for hippocampal volume loss remains unclear (Czéh & Lucassen, 2007; Duman, 2004).

Not only do hippocampal volumes differ in depressed individuals compared to non-depressed control participants, but neural activity differs as well. For instance, non-depressed control participants have greater fMRI activation in the hippocampus than depressed patients during verbal memory encoding tasks (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004) and associative encoding tasks (Fairhall, Sharma, Magnusson, & Murphy, 2010). Similarly, healthy controls' recollection memory performance correlates with fMRI activation in the right hippocampus and the right hippocampal head, but this effect is not observed in depressed individuals (Milne, MacQueen, & Hall, 2012).

In addition to volumetric changes and neural activity differences, neurotransmitters abnormalities have been implicated in the pathology of depression. Glutamate is the major

excitatory neurotransmitter in the human brain, and strict regulation is needed to maintain the delicate homeostatic balance with GABA the major inhibitory neurotransmitter. When the balance is upset excitotoxicity can occur and has been implicated in a number of disorders including depression (reviews by Mathews, Henter, & Zarate Jr, 2012; Yüksel & Öngür, 2010). For instance, when comparing depressed patients to healthy controls, glutamate and glutamine levels in the prefrontal cortex are reduced (Belmaker & Agam, 2008), cortical levels of glutamate and the enzyme that converts glutamate to glutamine are reduced (Choudary et al., 2005), and administration of ketamine (an NMDA antagonist) produces an immediate and long lasting antidepressant effect (Zarate Ca & et al., 2006). In the medial temporal lobe abnormalities in glutamate transmission have been associated with the pathophysiology of depression (Beneyto et al., 2007), and chronically depressed patients have significantly lower levels of glutamate/glutamine in the hippocampus than controls (Block et al., 2009; de Diego-Adeliño et al., 2012).

These abnormalities in glutamate levels are important in memory research because glutamate has significant effects on learning and memory (review by Riedel, Platt, & Micheau, 2003). For example, neuronal plasticity or long-term potentiation (a possible mechanism for memory), relies on glutamate and the activation of the NMDA receptor complex (Bliss & Collingridge, 1993). Memory encoding can be enhanced by drugs that facilitate glutamate transmission (Staubli, Rogers, & Lynch, 1994). Activity in the hippocampus, entorhinal, and parietal cortex, mediated by glutamate AMPA and NMDA receptors is necessary for memory consolidation (Izquierdo & Medina, 1997).

Pattern Separation and Neurogenesis

The process by which neurons are generated from progenitor cells after fetal development has ceased is called adult neurogenesis (Barlow & Targum, 2007). The dentate gyrus is one of only two known brain regions where neurogenesis continues in adults (the olfactory bulb is the other region) (Eriksson et al., 1998; Sahay, Wilson, & Hen, 2011). The rate of adult neurogenesis can be affected by a number of factors. Experiments on rodents have demonstrated that stress (E. Gould, Woolley, & McEwen, 1990) and aging (Kuhn, Dickinson-Anson, & Gage, 1996) decrease adult neurogenesis, whereas environmental enrichment (Kempermann, Kuhn, & Gage, 1997), physical activity (van Praag, Kempermann, & Gage, 1999), and antidepressants (Malberg, Eisch, Nestler, & Duman, 2000) increase adult neurogenesis. Autopsy studies support the idea that antidepressants may increase neurogenesis. Boldrini and colleagues (2009), found more neural progenitor cells (the proliferation level of progenitor cells determines the rate of neurogenesis) and larger dentate gyrus volume in depressed individuals who had been treated with antidepressants compared to individuals who had not been treated these findings suggest that individuals treated with antidepressants may have increased neurogenesis.

Neurogenesis is also affected by glutamate and how it acts on a number of different receptors (reviews by Nacher & McEwen, 2006; Zhao, Deng, & Gage, 2008). Deisseroth et al. (2004) showed that by stimulating adult hippocampal neuronal cells with glutamate, excitatory stimuli can act directly on adult hippocampal neuronal precursor cells to increase neurogenesis. NMDA receptors also play a role in the regulation of neural stem/progenitor cells migration (part of the neurogenesis life cycle), by increasing extracellular glutamate (by inhibition of its uptake), the rate of cell migration is accelerated. On the other hand cell migration is blocked by NMDA receptor antagonists (Komuro & Rakic, 1993).

These studies indicate that conditions often associated with depression may influence neurogenesis, yet a direct connection between depression and neurogenesis has not been demonstrated. Although the relationship between adult neurogenesis and depression remains unclear, the relationship between neurogenesis and pattern separation is more apparent. For example, when adult hippocampal neurogenesis is ablated, mice are unable to detect small changes in object presentation on a spatial navigation task (Clelland et al., 2009). Conversely, by augmenting the survival of adult-born neurons, mice with increased hippocampal neurogenesis have a greater ability to differentiate between overlapping contextual representations—a skill indicative of enhanced pattern separation (Sahay, Scobie, et al., 2011). These studies suggest that neurogenesis supports the process of pattern separation.

To summarize the literature presented so far, depression is associated with declarative memory impairments, smaller hippocampal volumes correlate with depressive episodes, smaller hippocampal volumes are associated with impaired declarative memory, and neurogenesis allows for pattern separation to occur. It still remains to be demonstrated whether depression negatively impacts pattern separation abilities. The present study will assess the relationship between depression and pattern separation abilities.

Hypotheses

We hypothesized that depressed individuals would have impaired pattern separation compared to non-depressed individuals. However, we are not suggesting that this relationship is a directly causal one. Rather, that any relationship between depression and pattern separation will provide indirect support for the hypothesis that depression decreases neurogenesis and that decreased neurogenesis, in turn, leads to impaired pattern separation abilities. That said,

neurogenesis was not measured in this study and any implications involving neurogenesis are based on past research.

To test this hypotheses we will administer a tests that has been used to measure pattern separation in humans (Kirwan & Stark, 2007). We anticipate that depressed individuals will perform worse on pattern separation tasks than non-depressed control participants matched for age, sex, and education level.

Methods

Participants

Ninety-eight participants (see table 1) gave written informed consent before participating. Participants were recruited from the Brigham Young University community and were awarded course credit. All participants indicated that they were educated at a college level (12-16) except one who had a master's level (16-18) education. Data from 15 participants were excluded due to antidepressant medication use, leaving data from 83 participants in the analysis.

Following the consent process, participants completed background questionnaires to assess factors known to affect adult neurogenesis: an exercise questionnaire, a questionnaire to determine anti-depressant use, the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) and the Pittsburgh Sleep Quality Inventory (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). To assess the depressed state of the participant the Depression Anxiety Stress Scales (Lovibond & Lovibond, 1995) was used. In the depression scale a score of 0-9 is considered normal or non-depressed, mild depression is 10-13, moderate 14-20, and a severe depressed score is 21 or above. In the present study there were: 87.5% of participants

were in the normal range, 4.2% were in the mild depression range, 4.1% were in the moderate depression range, and 4.2% were in the severe depression range,

Behavioral Procedure

The continuous recognition memory task was modeled after a task used in previous studies (Bakker et al., 2008; Duncan, Sadanand, & Davachi, 2012; Kirwan & Stark, 2007; Toner, Pirogovsky, Kirwan, & Gilbert, 2009) and utilized the self-paced version as used previously (see Toner, Pirogovsky, Kirwan, & Gilbert, 2009). Participants were shown a series of images of everyday objects while seated approximately two feet from a computer monitor. The stimuli were drawn from three groups: One group of images (Foils) only appeared once. A second group of images (Repeats) appeared twice throughout the study. The final group (Lures) consisted of paired images that were visually and conceptually similar (see Figure1). These images have been previously tested for similarity (Kirwan & Stark, 2007). The delay between first presentation and repeated presentation of lure and repeat images varied with a mean lag of 19 trials. For each image, participants were asked to determine if the image was new, similar, or old. If participants did not remember seeing the image before they were instructed to select "new." If they remember having seen a previous image that was similar but not exactly the same as the current image they were instructed to select "similar." If the image was exactly the same as a previous image they were instructed to select "old." Images remained on the screen until the participant made a selection. Participants viewed a total of 642 images in 6 blocks of 107. Participants were instructed that stimuli did not repeat across blocks.

Results

Figure 2 presents the mean proportion of "old", "similar", and "new" responses to first, repeated, and lure stimuli for all participants. Participants were very accurate at identifying first and foil image presentations as "new" (96.57%). Accuracy for the repeated image was also high (84.11%). Responses to the lure image were divided between correctly identifying them as "similar" (54.42%) and incorrectly calling them "old" (33.76%). This performance was similar to that observed previously (Kirwan & Stark, 2007).

Our question of interest was whether there was a relationship between depression and pattern separation performance. In our task, successful pattern separation is necessary to correctly identify the lure stimuli as "similar". Accordingly, we calculated a pattern separation score by taking the proportion of "similar" responses to lures and corrected for participants' response bias by subtracting the proportion of "similar" responses to first presentations, i.e., p("similar" | lure) – p("similar" | foil) (see Kirwan et al., 2012; Kirwan and Stark, 2007). In the present study pattern separation scores ranged from 0-72 [M = 44.67, SD = 16.385].

Correlation and multiple regression analyses were conducted to examine the relationship between scores on the self-report questionnaires and pattern separation scores. First we performed a correlation analysis to identify what independent measures were correlated with pattern separation scores (see table 2). There was a significant negative correlation between depression and pattern separation scores, indicating that the more participants felt depressed, the lower their pattern separation score, $r(81) = -.255$, $p < .05$. There was also a significant positive correlation between average reaction time (RT) and pattern separation score, $r(81) = .468$, $p <$

.001. There was no significant correlation between depression and average reaction time, $r(81) = -.071$, n.s.

We next conducted a simultaneous multiple regression analysis with pattern separation score as the independent variable and depression and RT as predictor variables. Depression significantly predicted pattern separation score ($\beta = -.223$, $p < .05$), as did average RT ($\beta = .452$, $p < .001$). The two predictors also explained a significant proportion of variance in pattern separation scores ($R2 = .269$, $F(2,80) = 14.707$, $p < .001$).

The relationship between RTs and pattern separation performance may have been driven by encoding effects, where longer exposures to stimuli during encoding lead to better recognition memory performance at retrieval or by effort during encoding or retrieval. To account for the effect of reaction time, we created a model that excluded data from participants who had mean RTs two standard deviations above the group mean (n=5). We also excluded participants who exhibited a lack of effort on the task by establishing "effort trials", which were repeat trials that were separated from the first presentation by 1-4 trials. We reasoned that scores less than 45% correct on these short-delay trials and average reaction times of less than one second were evidence of a lack of effort on the part of the participant. Data from six participants were excluded from this analysis for this reason (final $n = 72$).

A stepwise multiple regression was conducted to evaluate whether both depression and reaction time were necessary to predict pattern separation scores. At step 1 of the analysis, depression scores were entered into the regression equation and were significantly related to pattern separation scores, $F(1,70) = 8.801$, $p < .01$ (see Figure3). The multiple correlation coefficient was .11, indicating that approximately 11% of the variance of the pattern separation

scores could be accounted for by depression scores. Reaction time did not enter into the equation at step 2 of the analysis ($t(69) = 1.256$, $p > .05$), indicating that average RTs were not significantly related to pattern separation scores. The regression equation for predicting pattern separation score was: Predicted pattern separation score = -.757(depression score) + 48.89

Inspection of the relationship between pattern separation score and depression score indicated that an outlying participant might have unduly influenced the model. To control for this, we re-calculated the model while excluding the participant with the highest depression score. In the new model, depression scores significantly predicted pattern separation scores. ($p < .05$)

Discussion

Previous behavioral studies have associated memory impairments with depression (Burt et al., 1995; Zakzanis et al., 1998). In addition to these behavioral findings a growing body of evidence is associating depression with physiological changes in the brain. These physiological changes include: reduced hippocampal volume (Bremner et al., 2000; Campbell, Marriott, Nahmias, & MacQueen, 2004; Videbech & Ravnkilde, 2004), increased neurogenesis from antidepressant treatment (Boldrini et al., 2009; Malberg, Eisch, Nestler, & Duman, 2000), and reduced glutamate/glutamine levels (Belmaker & Agam, 2008; Beneyto et al., 2007; Block et al., 2009; de Diego-Adeliño et al., 2012) that have been known to affect neurogenesis (reviews by Nacher & McEwen, 2006; Zhao, Deng, & Gage, 2008). Additionally animal studies that use stress to mimic clinically relevant symptoms of depression have demonstrated a relationship between depression-like symptoms and reduced adult hippocampal neurogenesis (Eyre & Baune,

2012; Fournier & Duman, 2012; Hanson, Owens, & Nemeroff, 2011; Petrik, Lagace, & Eisch, 2012).

Even though past research has explored behavioral and physiological aspects of depression, the mechanisms behind these associations are not yet well understood. The present study examined the relationship between pattern separation performance and depression symptoms. The object discrimination task that we used has been shown to index pattern separation abilities in healthy younger adults (Bakker et al., 2008; Duncan, Sadanand, & Davachi, 2012; Kirwan & Stark, 2007; Toner et al., 2009). Performance on this task decreases with age (Toner et al., 2009; Yassa et al., 2011) and is impaired with hippocampal damage (Kirwan et al., 2012). The present study adds to this growing body of evidece by showing that pattern separation performance has a negative relationship with self-reported depression symptoms.

Computational models of the medial temporal lobe propose that the hippocampus is especially suited to perform pattern separation (Norman & O'Reilly, 2003), possibly due to neurogenesis in the dentate gyrus (Sahay, Wilson, & Hen, 2011). Consistent with this proposal, rodents with ablated or reduced neurogenesis are impaired at spatial pattern separation tasks (Clelland et al., 2009) while rodents with increased neurogenesis have superior pattern separation performance (Sahay, Scobie, et al., 2011). It has been suggested that hippocampal neurogenesis is reduced in depression, and this may be one potential mechanism underlying memory impairments in depression.

Our results are consistent with the hypothesis that a reduction in neurogenesis is related to depression symptoms and that neurogenesis is important for pattern separation performance.

Also consistent with this hypothesis is the effect of antidepressant use in our sample. When we included the data from participants who were being treated with antidepressants, the relationship between depression symptoms and pattern separation becomes non-significant. However without a sufficient sample size of participants being treated with antidepressants, the present study cannot determine if there is a relationship between groups. Accordingly, future research in this area is needed to better understand the behavioral effects antidepressants might have on pattern separation performance.

Recent studies have proposed that psychological disorders can result when the brain tends too readily or insufficiently toward pattern separation. In order to be effective, pattern separation must be sufficiently discriminative, but not overactive. Impaired pattern separation may result in an overgeneralization of environmental stimuli, a trait that may be seen in disorders such as anxiety, depression, and post-traumatic stress (Kheirbek et al., 2012; Lissek, 2012; Sahay & Hen, 2007). Our finding that depression symptoms are related to reduced pattern separation performance supports the theory that an inability to sufficiently discriminate stimuli could be used as a marker for certain psychological disorders such as depression. Conversely, disorders that exhibit excessive attention to detail such as autism or obsessive compulsive disorder could be indicative of overactive pattern separation. Future research in this area is needed to better understand behavioral differences in pattern separation for the various disorders implicated. For example an investigation in to anxiety disorders (such as post-traumatic stress disorder) that uses a pattern separation task with stimuli with varying levels of positive and negative valance along with fMRI analysis of activation in the sub-regions of the hippocampus might be able to delineate how hippocampal function is affected by these disorders.

Working with a student population for this study had several limitations: controls were in the normal range of depression, however the sample of depressed individuals was small and the mean score for depressed participants fell in the mild range of depression resulting in the need to use a regression model instead of a group mean comparison technique. Also, because we were used a measure of depressive symptoms and not a clinical diagnosis of depression, we were not able to account for the length of time participants had been depressed or the causes of depression. Despite these limitations, we found that depression is associated with pattern separation abilities. This behavioral finding is consistent with the neurobiology effects of depression. Furthermore, it is possible that depression is affecting neurogenesis (the suggested mechanism of pattern separation), and that this mechanism is responsible for the poor memory performance in depressed individuals. However we are not suggesting that this relationship is a directly causal one. Rather, the observed relationship provides indirect support for the hypothesis that depression decreases neurogenesis, which in turn, can lead to impaired pattern separation abilities. We suggest that future research in this area is needed to better determine the type of relationships between psychological disorders, pattern separation, antidepressants, and neurogenesis.

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Table 1

Demographics information of study participants (N=98)

	Averages		
		Mean	*SD*
	Age	20.79	5.13
	Anxiety[A]	5.43	5.22
	Depression[B]	6.70	7.97
	Stress[C]	9.46	7.09
	Frequency		
		Frequency	Percent
Sex			
	Male	31	32
	Female	67	68
Handedness			
	Right	87	89
	Left	11	11
Sleep Quality			
	Very good	29	30
	Fairly good	54	55
	Fairly bad	11	11
	Very bad	4	4
Exercise - Jogging			
	Never	12	12
	Less than Once a Month	14	14
	Once a Month	10	10
	2-3 Times a Month	16	16
	Once a Week	19	20
	2-3 Times a Week	21	21
	Daily	6	6

Note. [A]Anxiety score can range from 0 (normal) to 20+ (severe anxiety). [B]Depression score can range from 0 (normal) to 28+ (severe depression). [C]Stress score can range from 0 (normal) to 34+ (severe stress).

Table 2

Correlation Analysis (n=83)

	Pattern Separation Score	
	Pearson Correlation	Sig. (2-tailed)
Anxiety	-.106	.339
Depression	-.255	.020*
MDD	.116	.297
Bipolar	.152	.171
Survey Duration	-.099	.374
lifting Exercise	.022	.843
Aerobic Exercise	-.074	.505
Jogging Exercise	-.108	.332
Average Distance Jogging	.062	.577
Sleep Quality	-.077	.488
Sleep Medication	-.049	.657
Age	-.155	.162
Stress -State	-.101	.363
Stress -Trait	-.131	.238
Gender	-.132	.233
Reaction Time	.468	.000**

Note: *Significant at the $p<0.05$ level. **Significant at the $p<0.001$ level.

Figure 1. Example similar stimulus pairs. Initial stimuli (A) were followed after a variable lag by either an exact repeat or a lure stimulus (B), which were visually and conceptually similar to the first image. Participants were instructed to respond "new" to novel stimuli, "old" to exact repeats, and "similar" to lure stimuli.

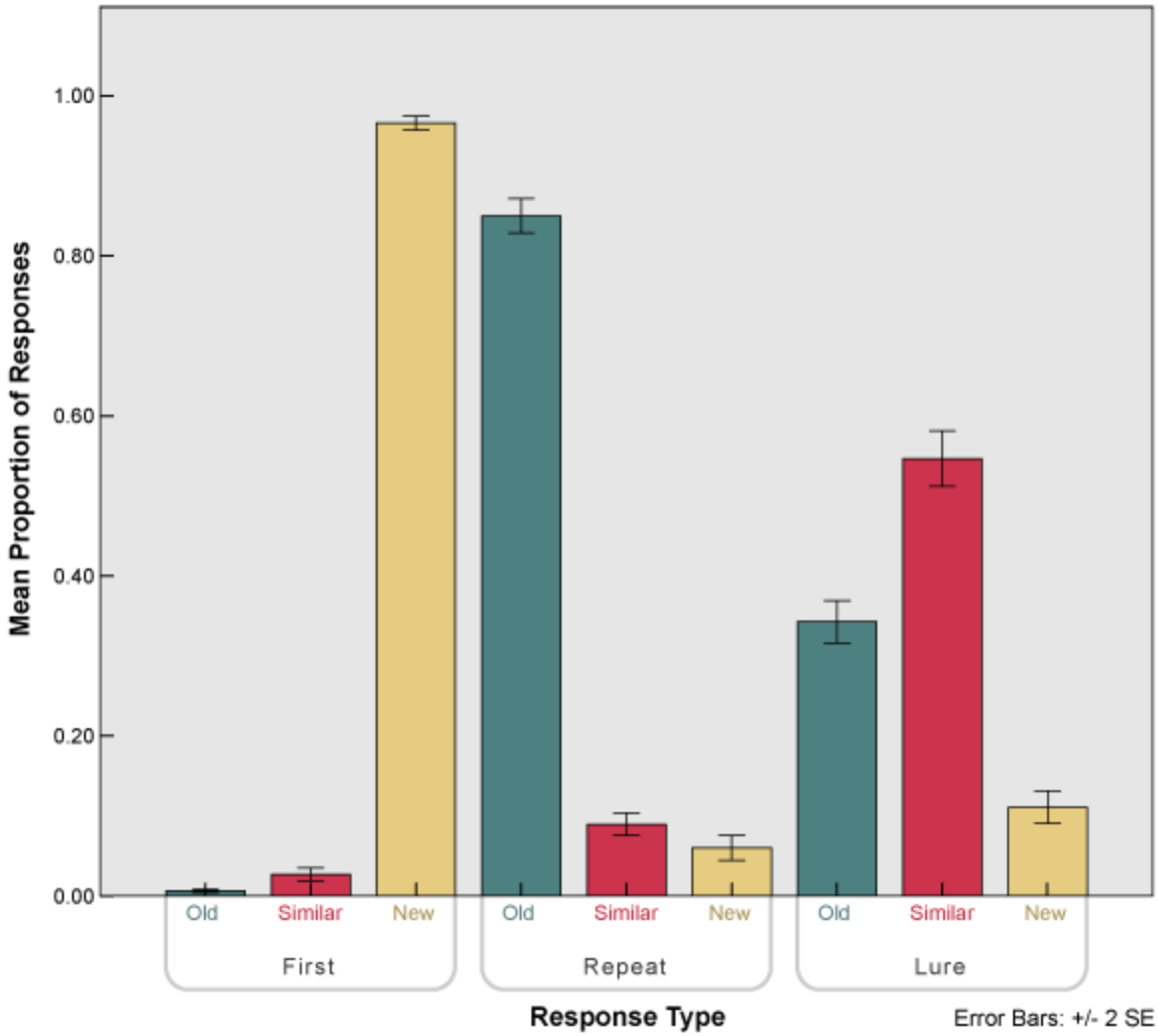

Figure 2. The mean proportion of responses for all participants. Responses types were old, similar, or new. Stimulus types were first (the first presentation of an object or a foil), repeat (objects presented previously during the experiment), and lure (objects that were similar to previously presented objects).

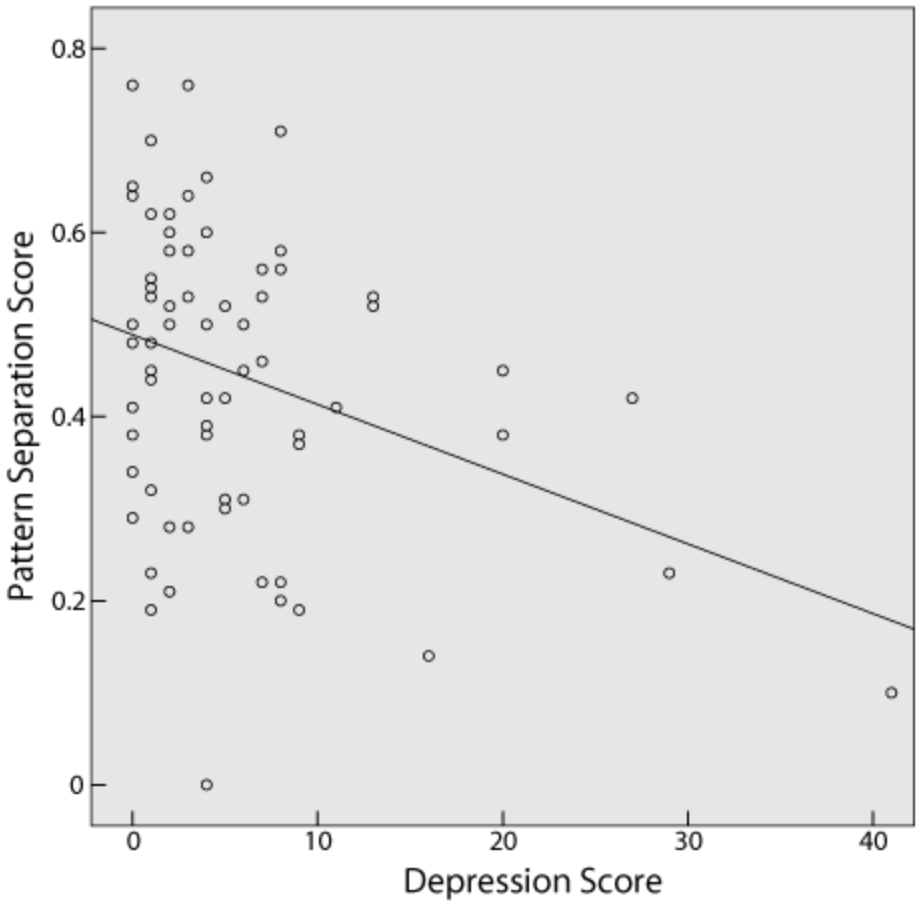

Figure 3. Scatterplot of pattern separation scores as a function of depression. Pattern separation scores were defined as the proportion of "similar" responses to lures corrected by the proportion of "similar" responses to foil stimuli.