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Research report

# A possible negative influence of depression on the ability to overcome memory interference

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## HIGHLIGHTS

- Computational models, research, and theoretical papers suggest a possible link between neurogenesis and pattern separation.
- Neurogenesis maybe reduced in depression, suggesting a possible impairment in pattern separation performance in depression.
- A behavioral pattern separation paradigm was used to test a large group of young adults.
- Self-reports of depression symptoms along with other factors known to affect neurogenesis were collected.
- We found a significant negative relationship between depression symptoms and pattern separation performance.

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## ABSTRACT

Pattern separation is a mechanism for encoding memories, 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 memory tasks requiring pattern separation is still unclear even though it is well established that depression is associated with reduced declarative memory performance and decreased hippocampal volume. Accordingly, we designed a study to investigate the relationship between pattern separation performance and the severity of depression symptoms in an otherwise healthy population. Participants completed a pattern separation memory test and a set of questionnaires to gauge their level of depression. We found a negative relationship between depression scores and pattern separation scores. These results provide support for the idea that depression is negatively related to pattern separation performance.



Memory impairments have been shown to occur in depressed patients [1], compounding an already devastating mental disorder. Some researchers estimate that within 20 years, depression will be the leading cause of disease burden in western nations, accounting for 5.7% of total disability adjusted life years, and the second leading cause of illness worldwide [2]. Though the association between depression and impaired memory performance is well documented, the mechanisms underlying this association are not yet well understood.

Depression does not affect all types of memory equally. It appears that memory impairments associated with depression are greater for declarative (or explicit) memory than non-declarative (or implicit) memory [1,3–5]. In a meta-analysis of studies with 726 patients with depression and 795 healthy controls, it was determined that depression had the largest adverse effect on episodic memory, and a significant, but less substantial, effect on semantic memory [3]. Spatial memory is also affected in individuals with depression. Patients with depression are poorer at spatial navigation in a virtual town navigation task than healthy comparison subjects [6]. Interestingly, declarative memory and depressed mood both improve with the administration of selective serotonin reuptake inhibitors (SSRIs) [7]. Memory deficits have also been observed in otherwise healthy young adults who have elevated depression scores (as measured by standard depression inventories) in tests such as delay-match-to-sample [8]. These studies demonstrate a clear link between depression and impaired declarative memory.

Studies reliably demonstrate that hippocampal volume is reduced in patients with depression compared to nondepressed controls [9–12]. This volumetric change is accompanied by impaired memory performance [13], and may be remitted by antidepressant use [14]. These changes in hippocampal volume have been 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

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unclear [15,16]. In addition to volumetric changes, neurotransmitter abnormalities have been implicated in the pathology of depression. In the medial temporal lobe, abnormality in glutamate transmission has been associated with the pathophysiology of depression [17]. Chronically depressed patients have significantly lower levels of glutamate/glutamine in the hippocampus than do nondepressed controls [18,19].

It has been suggested that depression-like symptoms affect neurogenesis [20–23]. Adult neurogenesis is the process by which neurons are generated from progenitor cells after fetal development has ceased [24]. The dentate gyrus is one of only two known brain regions where neurogenesis continues into and throughout adulthood [25,26]. The rate of adult neurogenesis can be affected by a number of factors. For instance, experiments with rodents have demonstrated that stress [27] and aging [28] decrease adult neurogenesis, whereas environmental enrichment [29], physical activity [30], and antidepressants [31] increase adult neurogenesis. In postmortem studies in humans, Boldrini et al. [32], found a greater number of neural progenitor cells and larger dentate gyrus volume in depressed individuals who had been treated with antidepressants compared to individuals who had not been treated, suggesting that individuals treated with antidepressants may have increased neurogenesis. These studies indicate that conditions often associated with depression may influence neurogenesis, although a direct connection between depression and neurogenesis has not been demonstrated in humans.

Not only does hippocampal physiology differ in depressed and nondepressed participants, but neural activity differs as well. For instatnce functional magnetic resonance imaging (fMRI) studies have shown that nondepressed participants have greater hippocampal activation than depressed patients during verbal memory encoding tasks [33] and associative encoding tasks [34]. 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 [35].

Taken together, the preceding data suggest that hippocampal structure and function are impacted by depression. Computational models of hippocampal function predict that depressed patients should be impaired at the computational process of pattern separation. This process is characterize by the ability to represent similar experiences or events as separate, non-overlapping representations [36–40] and relies on sparse representations in the dentate gyrus [36,38]. Accordingly, computational models predict that damage to the dentate gyrus should impair pattern separation performance. To test these predictions, Gilbert et al. [41] 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 performance of lesioned rats improved. These researchers later compared the effects of lesions on two different regions of the dorsal hippocampus: the dentate gyrus and CA1. Rats with lesions to the dentate gyrus were deficient on spatial pattern separation, but not temporal separation tasks. In contrast, rats with lesions to the CA1 were impacted on temporal but not spatial tasks [42]. Further studies have indicated that pattern separation is related to neurogenesis. For example, when adult hippocampal neurogenesis is ablated, mice are unable to detect small changes in object presentation on a spatial navigation task [43]. 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 [44].

Studies using behavioral measures and fMRI have been used to assess pattern separation processes in the human hippocampus. Kirwan et al. [45] 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 have demonstrated that the hippocampus is involved when pattern separation demands are high (e.g., [46]) and that the specific pattern of hippocampal activity depends on the current task demands [47]. Using an incidental pattern separation memory task, Bakker et al. [48] demonstrated that the dentate gyrus and CA3 are critically involved in the process of pattern separation (see also [49]).

In order to be effective, pattern separation must sufficiently discriminate but not be overactive. It has been suggested that psychological disorders are associated with disrupted pattern separation abilities [44,50]. Overactive pattern separation may hinder the normal cognitive process of integrating information from the surrounding environment, causing an individual to selectively focus on minute details that would go unnoticed by others. This cognitive difference could result in a behavioral fixation on minutiae as seen in autism or obsessive compulsive disorder [26]. Alternatively, insufficient pattern separation may result in excessive generalization, where an individual would associate moderately similar stimuli as equal, even though the stimuli have distinct differences. This overgeneralization could result in a maladaptive behavioral response to a stimulus, making a harmless item or event seem like a situation that had previously caused panic and fear, as in anxiety, panic, and post-traumatic stress disorder [51,52]. Depressed individuals tend to perceive stimuli in their environment as "similar" and have a bias toward making negative inferences about the self [53–55]. This negative overgeneralization might help explain the anhedonia and lack of interest in new experiences experienced by depressed individuals [26]. The pathology of this tendency to overgeneralize (i.e., hypoactive pattern separation) seen in some mood disorders has been associated with the hippocampus and its subregions [56,57]. Accordingly, impairments on a pattern separation task might be an indicator for both the behavior and underlying pathophysiology of these psychological disorders. This theory implies a relationship between depression-like symptoms and pattern separation. If true, this theory could have far-reaching implications in helping researchers better understand the mechanisms involved in depression. Recently, Déry et al. [58] examined the pattern separation performance of two healthy adult groups. One group was tested on a pattern separation task before and after taking part in a six-week aerobic exercise regime. Participants who experienced a change in fitness level had a greater degree of change on the pattern separation task than those who did not experience a change in fitness level. The authors attribute this change in performance to the exercise-induced increase in hippocampal neurogenesis. Similarly, the second group of participants completed a self-report depression scale and a pattern separation task. The authors found that participants who had lower depression scores performed significantly better on a pattern separation memory task, presumably due to lower levels of neurogenesis associated with more depression symptoms.

Here, we sought to further investigate the relationship between depression symptoms and pattern separation performance. In order to expand on previous research, we collected measures of mood (i.e., depression and anxiety) as well as self-reported measures that assessed other factors know to affect neurogenesis, such as exercise and antidepressant use. In order to test the predictions of computational models regarding the relationship between pattern separation and depression symptoms (and the putative associated decrease in hippocampal neurogenesis), we gathered measures from a group of healthy younger adults who had a range of depression ratings. Depression, anxiety, and other measures