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Higher depression scores are associated with lower pattern separation performance in humans

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Abstract

Memory impairment has been connected to depression, however this association appears complex. Pattern separation is a specific hippocampal function, which separates similar events and stimuli into distinct memory representations. Hippocampal volume reduction has been seen in individuals suffering from depression. Multiple rodent studies have shown that adult neurogenesis in the dentate gyrus of the hippocampus is crucial for proper pattern separation. There are several factors that are thought to influence neurogenesis. For example stress, depressive symptoms and aging have a negative effect on neuronal plasticity. On the other hand, exercise and antidepressants seem to accelerate neurogenesis. Patients with hippocampal damage are impaired in the pattern separation tasks, but not in the recognition memory tasks. Few studies have investigated the direct relationship between depression and pattern separation in humans. The current study addressed this issue by testing Swedish University students. We found a negative correlation between depression scores and pattern separation performance. The correlation between depression scores and recognition memory was not significant. Thus, we argue that depression is linked to impaired pattern separation ability. Unexpectedly, a gender-difference in pattern separation in favor of female subjects was found. We suggest that this issue should be investigated further by future studies.

Keywords: depression, pattern separation, memory interference, recognition memory, BPS-O, neurogenesis, hippocampus, dentate gyrus, gender, gender-difference.

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Introduction

Depression can be a very detrimental disorder. In the Swedish population, at least 25 % of all women and 15 % of men are expected to need treatment for depression at some point in their lives (Socialstyrelsen, 2010). For those affected by the disorder, the ability to perform even the most basic of daily tasks can become significantly disrupted. In addition to this, there is a moderately high co-morbidity between depression and other psychiatric disorders and somatic illnesses. Depression is also associated with higher suicide rates and mortality. At a societal level, depression places great economic strain on the health care system (Socialstyrelsen, 2010). Given the impact of depression on the individual, those closely related to the individual, and society as a whole, it is essential to better understand the psychopathology of this condition in order to develop enhanced treatment plans.

Depression has been clearly linked to memory impairment (Burt, Zembar, & Niederehe, 1995). Even though this link is relatively well established, the exact mechanisms are not completely understood and the association seems to be quite complicated. Individuals affected by depression have been shown to demonstrate weakened performance in tasks testing explicit memory, but not implicit memory (Burt et al., 1995; Elderkin-Thompson, Moody, Knowlton, Hellemann, & Kumar, 2011; Ellwart, Rinck, & Becker, 2003). A meta-analysis on depression and executive cognitive functions showed that depression severity was connected to impairment in episodic memory, cognitive function and processing speed, but not to visuo-spatial or semantic memory, however this study had its limitations due to the small amount of papers included (McDermott & Ebmeier, 2009). According to another meta-analysis, patients with a depressive disorder were impaired with regard to autobiographical

memory (Liu, Li, Xiao, Yang, & Jiang, 2013). Depression was also linked to overgeneralized and less specific autobiographical memories, whilst recollection was found to be slower in depressed individuals compared to the controls. Also, otherwise healthy young adults with high depression scores, as measured by the Beck's Depression Inventory (Beck, Steer, & Brown, 1996), showed a significantly poorer performance on a delayed match to sample memory test (Becker, MacQueen, & Wojtowicz, 2009).

For a long time the hippocampus has been believed to be a crucial brain structure for various declarative memory functions. It is involved in the formation of new associative memories, organizing representations of events into sequences and creating meaningful association networks. There is a dynamic communication between the hippocampus and the cerebral cortex, where the individual memory representations are stored. This communication is important for proper recollection. Moreover, through the repeated activation of these inter-cerebral pathways, the hippocampus can consolidate old memories and incorporate new information to previous representations (Eichenbaum, 2004).

There is a great deal of evidence to suggest that the hippocampus is involved in the pathophysiology of depression. Patients with depression have lower hippocampal volumes compared to controls (Bremner et al., 2000; Campbell, Marriott, Nahmias, & MacQueen, 2004; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Videbech & Ravnkilde, 2004) Interestingly, the amount of depressive episodes correlated with the right-sided hippocampal volume reduction, but not with the left-sided hippocampus size (Videbech & Ravnkilde, 2004). Additionally, it has been found that hippocampal volume loss is connected to verbal memory impairment, whilst the overall brain size and intellectual performance did not seem to be affected (Sheline, Sanghavi, Mintun, & Gado, 1999). Antidepressants are suggested to have a neuroprotective role against hippocampal volume loss in patients suffering from depression (Sheline, Gado, & Kraemer, 2003).

There are two noteworthy functions of the hippocampus that were first introduced by David Marr (1971) and are relevant to mention here. Pattern completion is the process of making overlapping stimuli even more similar, helping to generalize stimuli when encoding them into memory. This is especially important when a disturbance is present or when cues are imperfect. Pattern completion is also essential for successful memory retrieval. Nonetheless, pattern completion can lead to errors in recognition by not separating similar representations effectively. Thus, an opposing strategy to pattern completion i.e. pattern separation is needed. Because of pattern separation, overlapping representations can be made less similar. This function is important when two or more stimuli are very much alike and it is essential to make a clear distinction between these stimuli in order to form accurate memory representations (Marr, 1971). If this strategy did not exist, new memories could overwrite old ones, leading to interference and improper functioning. Pattern completion and pattern separation can be regarded as complementary learning systems, and both are important for proper memory function (McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003).

According to both Marr's and various other computational models, pattern separation is theorized to be performed by the dentate gyrus (DG) of the hippocampus (Marr, 1971; McClelland et al., 1995; McNaughton & Morris, 1987; Norman & O'Reilly, 2003; O'Reilly & Norman, 2002). Pattern completion, on the other hand, has been linked to another area in hippocampus; the CA3 (Marr, 1971). It is quite likely that the high turnover and production of new neurons in the DG throughout life could contribute to keeping similar memory representations separate (Becker, 2005).

It has been proposed that the granule cells of the DG are particularly responsible for pattern separation. These neurons have some qualities that make them well-suited for performing this function. There are a vast amount of granule cells in the rat DG (Amaral,

Ishizuka, & Claiborne, 1990) and their connections to CA3 are highly divergent (Leutgeb, Leutgeb, Moser, & Moser, 2007). They also have relatively low activity levels and high spatial selectivity (Barnes, McNaughton, Mizumori, Leonard, & Lin, 1990).

Throughout life, new neurons are produced from progenitor cells by the process of adult neurogenesis (Ming & Song, 2011). The DG is one of the two brain areas thought to be capable of this process (Eriksson et al., 1998; Sahay, Wilson, & Hen, 2011). There are several rodent studies suggesting that neurogenesis in the DG is crucial for proper pattern separation. It leads to newborn granule cells that seem to have a central role in pattern separation (Clelland et al., 2009; Sahay, Scobie, et al., 2011; Tronel et al., 2012). It also appears that the mature granule cells, which possibly comprise 90-95 % of all granule cells, are "retired" and are not involved in the encoding of new information (Alme et al., 2010). The mature neurons might be responsible for new learning only in old, familiar contexts and would not be involved in learning about the novel environment itself (Aimone, Deng, & Gage, 2010). It is postulated that the immature newborn granule cells, which constitute the minority of DG neurons, are the main functional neuronal population and thus responsible for pattern separation (Alme et al., 2010). Ablating neurogenesis seems to be associated with significant problems in pattern separation. Reduced neurogenesis in animals leads to problems in distinguishing between odors (Luu et al., 2012) and visual cues (Winocur, Becker, Luu, Rosenzweig, & Wojtowicz, 2012). Lesion studies show that damaging the DG in rodents leads to impairments in spatial pattern separation (Gilbert, Kesner, & Lee, 2001; Kesner, Lee, & Gilbert, 2004). In light of this evidence it seems that neurogenesis in the DG is necessary for proper pattern separation ability.

Neurogenesis in the DG and pattern separation ability may play quite a significant role in mood-regulation. Depression symptoms have been linked to reduced neurogenesis in the DG of rodents (Eyre & Baune, 2012; Fournier & Duman, 2012; Hanson,

Owens, & Nemeroff, 2011; Petrik, Lagace, & Eisch, 2012). Also other factors such as stress (Cameron & Gould, 1994; Gould, Woolley, & McEwen, 1990) and aging (Kuhn, Dickinson-Anson, & Gage, 1996) reduce neurogenesis. Old rats' pattern separation abilities seem to be impaired, since they show difficulty navigating in similar, but alternative environments (Wilson et al., 2004; Wilson et al., 2003). This impairment may be caused by a shift towards a more active pattern completion, making old memory processing the more dominant function of the hippocampus, subsequently making it harder to encode new memories (Wilson, Gallagher, Eichenbaum, & Tanila, 2006; Wilson, Ikonen, Tanila, Gallagher, & Eichenbaum, 2005). There is some evidence to suggest that even alcohol and nicotine can diminish neurogenesis in the DG (Jang et al., 2002; Morris, Eaves, Smith, & Nixon, 2010).

On the other hand, factors such as environmental enrichment (Kempermann, Kuhn, & Gage, 1997), physical activity (Van Praag, Kempermann, & Gage, 1999) and long-term antidepressant treatment (Malberg, Eisch, Nestler, & Duman, 2000) are connected to increased neurogenesis in the DG. Boldrini et al. (2009) conducted a post-mortem study on individuals who had suffered from a major depression disorder. They found that patients who had been treated with antidepressants had a higher number of neural progenitor cells and larger DG volumes than patients who did not undergo the same treatment (Boldrini et al., 2009).

The evident ethical problems regarding the usage of invasive research techniques on humans make it hard to study neurogenesis and DG activity in the human hippocampus. To test behavioral pattern separation, Kirwan and Stark (2007) developed a computerized cognitive task ("pattern separation task"), where the research subjects are presented with pictures of everyday objects. Some of these objects are repeated across trials and called "repetitions" or "targets". Some objects are very similar, but not identical to the previously seen images and are named "lures". Some objects are completely new and are

referred to as “foils”. The subjects are asked to determine which category the viewed items fit into. In essence, the basic reasoning is that correctly identifying repetitions as previously seen i.e. “old” images reflects the recognition memory performance. On the other hand, correctly identifying lure images as “similar” reflects the pattern separation ability (Kirwan & Stark, 2007). Since then, modifications of this task have been developed and used to test pattern separation in humans.

Coarse measures of brain activity can be obtained with fMRI. Bakker et al. (2008) presented the first direct evidence that indicated the existence of pattern separation in the human hippocampus. Subjects’ brain activities were measured using a high-resolution fMRI camera whilst they performed a behavioral pattern separation task. It was reasoned that if an area in hippocampus or the medial temporal lobe is involved in pattern separation, its reaction to a lure stimuli would elicit activity similar to when an object is presented for the first time. On the contrary, if the brain area were to perform pattern completion, its reaction to lure stimuli would be consistent with brain activity seen during repetition. The results of this study showed that a bias toward pattern separation was present in the CA3/DG area of the hippocampus and a bias towards pattern completion was seen in the CA1 sub-region of the hippocampus and other areas of the medial temporal lobe (Bakker, Kirwan, Miller, & Stark, 2008). Likewise, further fMRI studies have shown that the human hippocampus plays a key role in successful pattern separation. The activation pattern in the medial temporal lobe is coherent with the predictions of the computational models i.e. the DG area shows more activity during pattern separation tasks, whilst other areas of the medial temporal lobe are more active during recognition memory tasks. Moreover, there seems to be a different pattern of hippocampal activation depending on different trial types mirroring recognition memory, pattern separation and the correct identification of foil stimuli as new (Kirwan & Stark, 2007). Motley and Kirwan (2012) also found that hippocampal pattern separation was lateralized;

semantic tasks showed more activation of the left hippocampus, whilst processing spatial information elicited more activity in the right hippocampus (Motley & Kirwan, 2012).

Effects of age on pattern separation have also been seen in studies on humans. Brain imaging studies by Yassa et al. (2011) show that older adults are impaired when it comes to correctly identifying lure stimuli as similar, suggesting an impairment in their pattern separation abilities. The pattern of activated brain areas was consistent with those suggested by animal models. It was also found that older individuals need higher dissimilarity between stimuli in order to encode new information as separate from previous representations (Yassa et al., 2011). An important study examined pattern separation and other memory functions in patients with hippocampal damage. The patients with hippocampal damage did not differ from the controls when it came to recognition memory. They were, however, less likely to correctly identify lure images as similar, implying that these patients had impaired pattern separation ability (Kirwan et al., 2012).

Although plausible, the direct link between depression and impaired pattern separation in humans needs confirmation through rigorous scientific testing. It has been suggested that psychological disorders can, to some degree, be explained by impaired pattern separation (Lissek et al., 2009; Sahay, Scobie, et al., 2011). It appears that just the right amount of pattern separation activity is needed for proper functioning. It has been suggested that exaggerated changes in neurogenesis could lead to psychopathological changes. An overactive pattern separation might hinder normal pattern completion and lead to a fixation toward unnecessary details, a phenomenon seen for example in the autism spectrum disorders (Sahay, Wilson, et al., 2011). On the other hand, the excessive generalization seen in anxiety disorders could be influenced by insufficient pattern separation (Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Sahay, Wilson, et al., 2011). This overgeneralization can lead to associating fear with stimuli that are similar to the conditioned danger cues, stimuli that

would not otherwise be seen as a threat. This overgeneralized fear-conditioning is seen in individuals suffering from anxiety disorders, posttraumatic stress disorders and panic disorders (Lissek, 2012).

Individuals affected by depression tend to have more negative overgeneralization about the self (Epstein, 1992; Ganellen, 1988). Negative feedback or criticism is generalized to apply to other aspects of personality (Kernis, Brockner, & Frankel, 1989). Moreover their recollection of autobiographical events is overgeneralized, especially when it comes to positive events (Brittlebank, Scott, Williams, & Ferrier, 1993). Insufficient pattern separation that leads to overgeneralization could also help explain why many individuals with depression show an inability to experience pleasure (Sahay, Wilson, et al., 2011). It has been theorized that this overgeneralization and impaired ability to form highly specific contextual memories is linked to the hippocampus and its sub-regions (Becker & Wojtowicz, 2007). Thus it can be said that impaired pattern separation is one of the explanatory factors for these kinds of mood-disorders both on a behavioral and neurobiological level (cf. Shelton & Kirwan, 2013).

Two recent studies managed to demonstrate a link between depression and pattern separation in humans. Déry et al. (2013) used cognitive behavioral tasks to test their research participants' visual pattern separation, recognition memory and reaction to novel stimuli. In their first experiment, they found that research participants who underwent a six-week exercise period, showed an improvement in their visual pattern separation ability. This improvement was strongest in those participants who had the greatest change in their fitness level. It was suggested that there was an increase in hippocampal neurogenesis due to exercise. In their second experiment the authors found that higher depression scores in otherwise healthy adults, as measured by the Beck's Depression Inventory, predicted poorer performance in visual pattern separation (Déry et al., 2013). A recent study by Shelton et al.

(2013) used a similar object discrimination task and found comparable results i.e. an association between higher depression scores and poorer pattern separation ability. They also administered other questionnaires regarding anxiety, exercise and sleep habits. No significant correlations between these other factors and pattern separation were found, indicating that poorer pattern separation in depression-prone individuals could be primarily connected to depression itself (Shelton & Kirwan, 2013).

The purpose of this study is to further investigate the relationship between depression symptoms and pattern separation, since there are only a few studies that have studied this link in human subjects (Déry et al., 2013; Shelton & Kirwan, 2013). The main hypothesis is that subjects who score higher on Beck's Depression Inventory would have a lower performance on a computerized behavioral task testing pattern separation, but not on the recognition memory task. Thus we expect a negative correlation between BDI scores and pattern separation, and a non-significant correlation between BDI scores and recognition. Since it was found that exercise could enhance pattern separation performance (Déry et al., 2013), we also want to test if a proxy measure of physical fitness i.e. Body Mass Index (BMI)(Keys, Fidanza, Karvonen, Kimura & Taylor, 1972) correlates with either pattern separation or recognition memory performance.

Method

Participants

Eighty-four volunteers were recruited for this study. Recruitment was conducted by setting out flyers at Lund University's biomedical campus ("BMC") and at student housing areas in Lund. The information presented on the flyers was also spread via "Facebook" and e-mails to students at Lund University. The participants were offered coffee and pastries as

compensation for their participation. Furthermore, they were included in a lottery in which three gift cards could be won (500 kr for groceries, 500 kr for Amazon and one month's Netflix membership).

Two of the eighty-four research participants (number 32 and 33) were completely excluded from the study, because the results from their computerized memory tests did not register onto the computer file. Thus in total eighty-two research participants were included in the study (50 male, 31 female and 1 missing value). The average age of the participants was 22.9 (*SD*=3.2*,* range: 19-37) Most participants were students at the medical faculty of Lund University, Sweden, but some other fields of studies were also represented. Some of the research participants were using psychotropic medication at the time of the study (please see Table X in the Appendix, pages 43-44).

Apparatus and Materials

The participants performed a "Behavioral Pattern Separation: Object task" (BPS-O) on a Toshiba laptop. This test is a valid behavioral task intended to test pattern separation in humans. The completion of this task takes 15 minutes. The stimuli consisted of pictures of everyday objects that were shown on a colored 17´´ screen. Each picture was shown for 2 s and there was a 0,5 s interval between pictures (Stark, Yassa, Lacy, & Stark, 2013) (The BPS-O program is available for download at the following web page: http://darwin.bio.uci.edu/~cestark/BPSO/bpso.html). Becks Depression Inventory- II (BDI–II) (Beck et al., 1996) –sheet was used for depression evaluation. BDI is a reliable and frequently used instrument for measuring depression. It consists of 21 items and is completed in around 5 minutes (Beck et al., 1996). A questionnaire regarding participants' gender, age, height, weight, previous depression diagnoses/episodes and usage of psychotropic medication was administered in paper form. The following formula was used to calculate the BMI of each

participant: (Weight in Kilograms) / (Height in Meters x Height in Meters))(Keys et. al., 1972). At the end of the questionnaire there was a space for additional commentary. The top part, which included questions regarding participants' personal information, was cut off in order to ensure that the data remained anonymous (see Appendix, pages 41-42). This part of the questionnaire was used for the lottery of gift cards.

Procedure

The design of the study was correlational with the main purpose to test associations between depression inventory scores, pattern separation and recognition memory.

The participants were told they were going to take part in a psychological study that would test their cognitive abilities. Firstly they were tasked with completing a computerized behavioral task and thereafter two different questionnaires. This information was provided both orally and through an informed consent form, which the participants were asked to sign (see Appendix, pages 45-46). Participants performed the experiment tasks alone in a quiet room without any disturbance.

In the first part of this study the research subjects engaged in a computerized behavioral test, BPS-O, in order to test pattern separation skills. The instructions for this test were given orally to the participant. The given information was in accordance with the official written instructions that follow the BPS-O –program (see Appendix, pages 47-48).

BPS-O is comprised of two phases. It was very important not to reveal that the computerized test also involved a second phase, which would test participants' memory. The first phase of the task was merely an encoding phase. It took 5 minutes to complete. The participants were shown a series of 128 images. The research participants needed to decide whether the items depicted on the images were "indoor" or "outdoor" objects by pressing different keys on the computer keyboard (V-key for "indoor", N-key for "outdoor"). A paper

note was placed at the lower part of the computer screen as a reminder of what the two different keys stand for.

After completing the first phase of the BPS-O, the study subjects were told that they would be tested for their memory with regards to the images they had just seen. This phase would take 8 minutes to complete. The participants were told they would see a series of pictures again. This time they had to choose if the picture on the computer screen was "old", "similar" or "new". It was communicated to each participant that the image was considered "old", if they had seen the exact same image in the first part of the behavioral task and "new" if the participant did not remember seeing the picture. The image was to be labeled "similar", if it was considered alike some image from the previous part of the behavioral task. The experiment subjects were instructed to press different keys on the keyboard to indicate the nature of the picture (V-key for “old”, B-key for “similar” and N-key for “new”). Before starting this second phase of the BPS-O -test, the participants were shown an official BPS-O instruction video to clarify the experiment procedure (the instruction video follows with the BPS-O program). Again a paper note was placed as a reminder for the participants. The pictures were shown in a randomized manner generated by the BPS-O –program. All in all, 192 images (64 "old", 64 "similar" and 64 "new" images) were presented to each participant. For illustration of the BPS-O -task paradigm, please see Figure 1. For examples of different similar stimulus pairs, please see Figure 2.

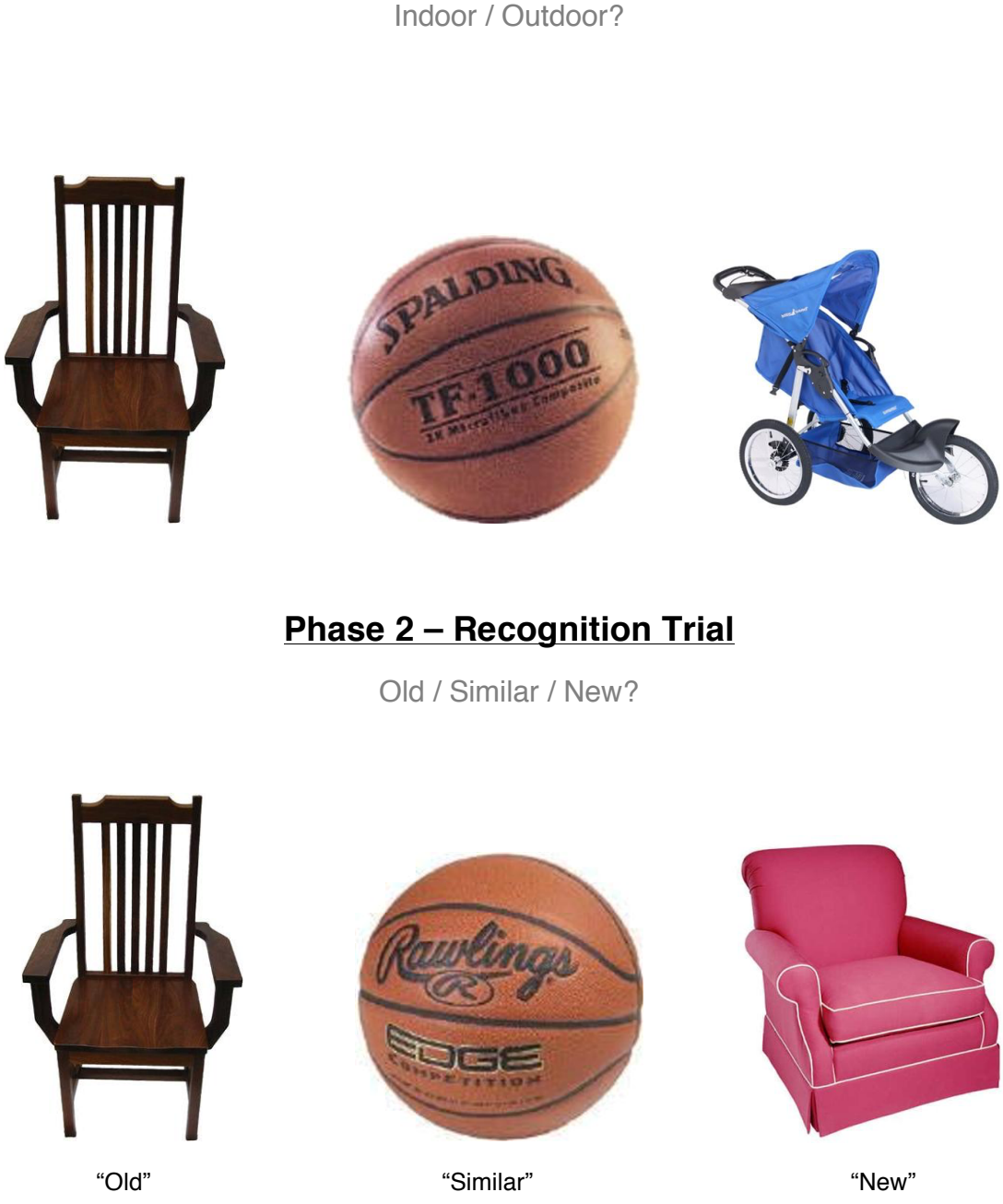

Figure 1. The BPS-O task paradigm. In the first phase of the behavioral pattern separation task, the participants are presented with a series of items. In the second phase, the items presented could either be "old" (exactly the same as a previously seen stimulus), "similar" (alike, but not identical to a previously seen stimulus) and "new" (a completely novel item).

Initially presented stimuli

Lure stimuli

Figure 2. Different examples of similar stimulus pairs. This figure illustrates the similarity level between initially presented stimuli and lure stimuli (stimuli highly similar to initially presented items) of the BPS-O task. The stimuli can differ from each other for example regarding color, orientation and small details.

After completing the BPS-O –task, the participants were to do the second part of this study, which involved filling out the two different questionnaire sheets. First the study subjects were administered a BDI–II in order to measure the subjects' depression scores. Thereafter, the participants filled out the second questionnaire (see section “Apparatus and Materials”, see Appendix, pages 41-42).

After having completed the whole experiment, the participants were offered some coffee and pastries. At this point the experiment leader also provided a short debriefing relating to the experiment. It was also explained why the true cause of the experiment could not be revealed in the beginning of the experiment. The study subjects' reactions were taken into consideration in order to make sure the experiment had not been upsetting to them.

Results

It was decided to use a one-tailed correlational, since the hypothesis was directed; Higher BDI scores would be associated with poorer performance in the pattern separation test but not in the recognition test. It seemed unreasonable to assume that low BDI would be associated with better performance in pattern separation tests. The level of statistical significance was set at $p< 0,05$, in line with previous studies (Déry et al., 2013; Shelton & Kirwan, 2013).

The SPSS program was used for each statistical calculation. For information about the demographic properties of the study population, please view Table 1. The answers from the self-constructed questionnaire were summarized in form of frequencies in Table X (please see Appendix, pages 43-44).

Table 1

Demographics of the Study Population

Averages	*M*	*SD*	*N*
Age	22.9	3.2	80[a]
Depression[b]	8.9	6.3	82
Body mass index (BMI)[c]	22.6	2.7	82

[a] Two of the participants failed to answer this question.
[b] Depression score range is 0-63 with the following cutoffs; 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression and 29-63 severe depression.
[c] BMI = (Weight in Kilograms / (Height in Meters x Height in Meters))

The BPS-O –program generated the response data of every participant. Figure 3 illustrates the average proportions of different responses (“old”, “similar”, “ new”) to different kinds of stimuli (“target”, “lure”, “foil”) across the study population as a whole. Response pattern was in accordance with similar previous studies (Déry et al., 2013; Shelton & Kirwan, 2013). The overall accuracy of identifying target stimuli as “old” was 77.3 %, *SD*=15.6%. The participants were also precise at identifying the foil stimuli as “new” (*M*=75.7 %, *SD*=12.9%). The accuracy of correctly identifying lure stimuli as “similar” was 46.8 %, *SD*=14.5% and incorrectly as “old” was 37.5 %, *SD*=12.2%.

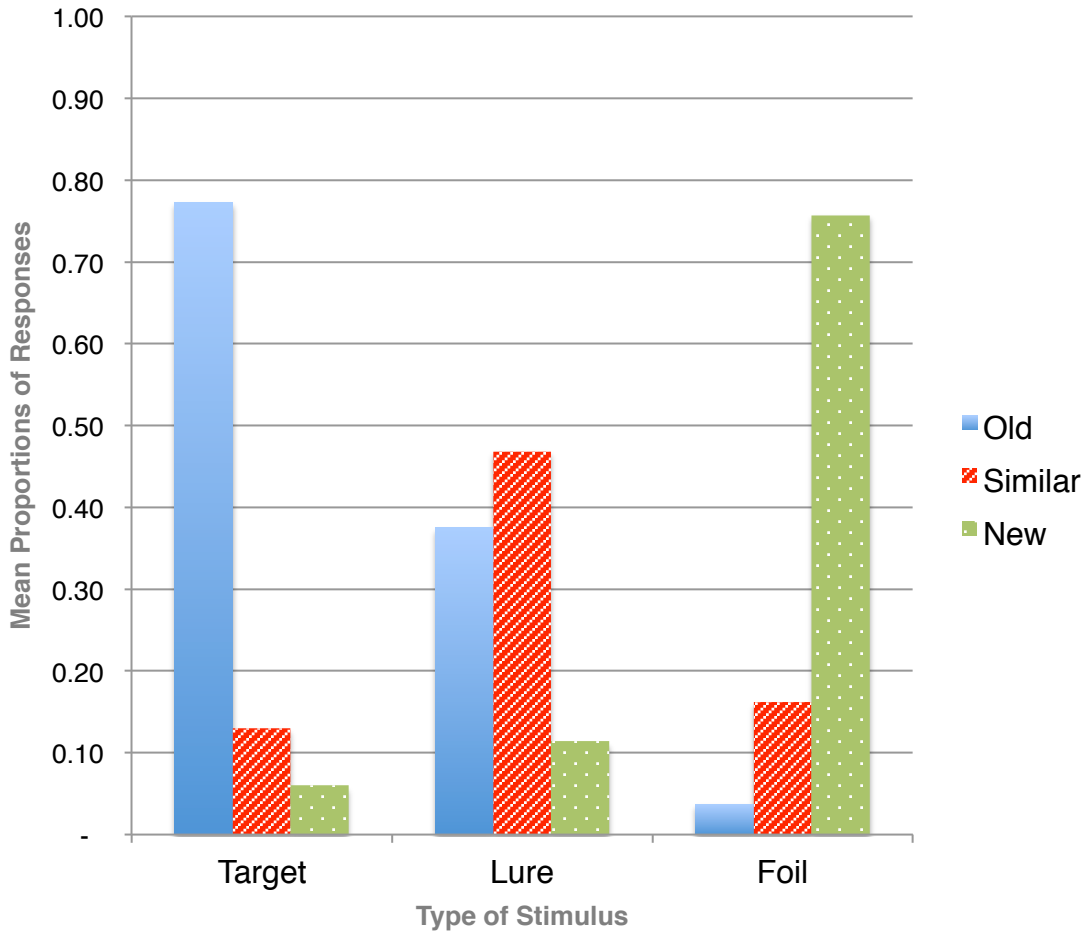

Figure 3. Proportions of different responses on the pattern separation task. This figure illustrates the mean proportions of responses ("old", "similar", "new") to different stimulus types (target=repetition item, lure= a stimulus almost identical to the repetition, foil= novel stimulus) for the study population as a whole.

In the behavioral task successful pattern separation is defined as correctly identifying lure stimuli as "similar". The final value for pattern separation is obtained by correcting participants' response bias by subtracting the proportion of "similar" responses to foil stimuli from the proportion of "similar" responses to lure stimuli i.e. p("similar" | lure) − p("similar" | foil). This corrected pattern separation value was calculated for each participant. A corrected value for recognition memory was calculated in a similar fashion i.e. p("old" | target) − p("old" | foil) (Déry et al., 2013; Kirwan et al., 2012; Kirwan & Stark, 2007). Mean values

for variables pattern separation (*M*=0.31, *SD*=0.16) and recognition Memory (*M*=0.74, *SD*=0.15) were calculated.

The next focus of interest was to obtain correlations regarding BDI-pattern separation and BDI-recognition memory. Scatterplots for BDI-pattern separation and BDI-recognition were generated that showed linear tendencies in both cases. The data for pattern separation, recognition and BDI variables was tested for normality. Pattern separation and recognition memory variables showed *sig*. 0.00, which indicated that these variables were not normally distributed. BDI showed *sig.* 0.78 purposing the normal distribution of this data. The overall evaluation was that the data did not meet the assumption of the normality of data.

Accordingly, a nonparametric test, Kendall's tau-b, was used for the correlational analysis. A one-tailed analysis was used, since the hypothesis was clearly directed. A weak negative correlation between BDI scores and pattern separation performance, $r(80)= -0.14$, $p=0.036$, 1-tailed, $R^2= 0.019$, was revealed. The correlation between BDI scores and recognition memory as well as the correlation between pattern separation and recognition memory were not statistically significant (r (80)=-0.080, p=0.15, 1-tailed; r (80)=0.075, p =0.16, 1-tailed). The main results are illustrated with the help of scatterplots in Figure 4.

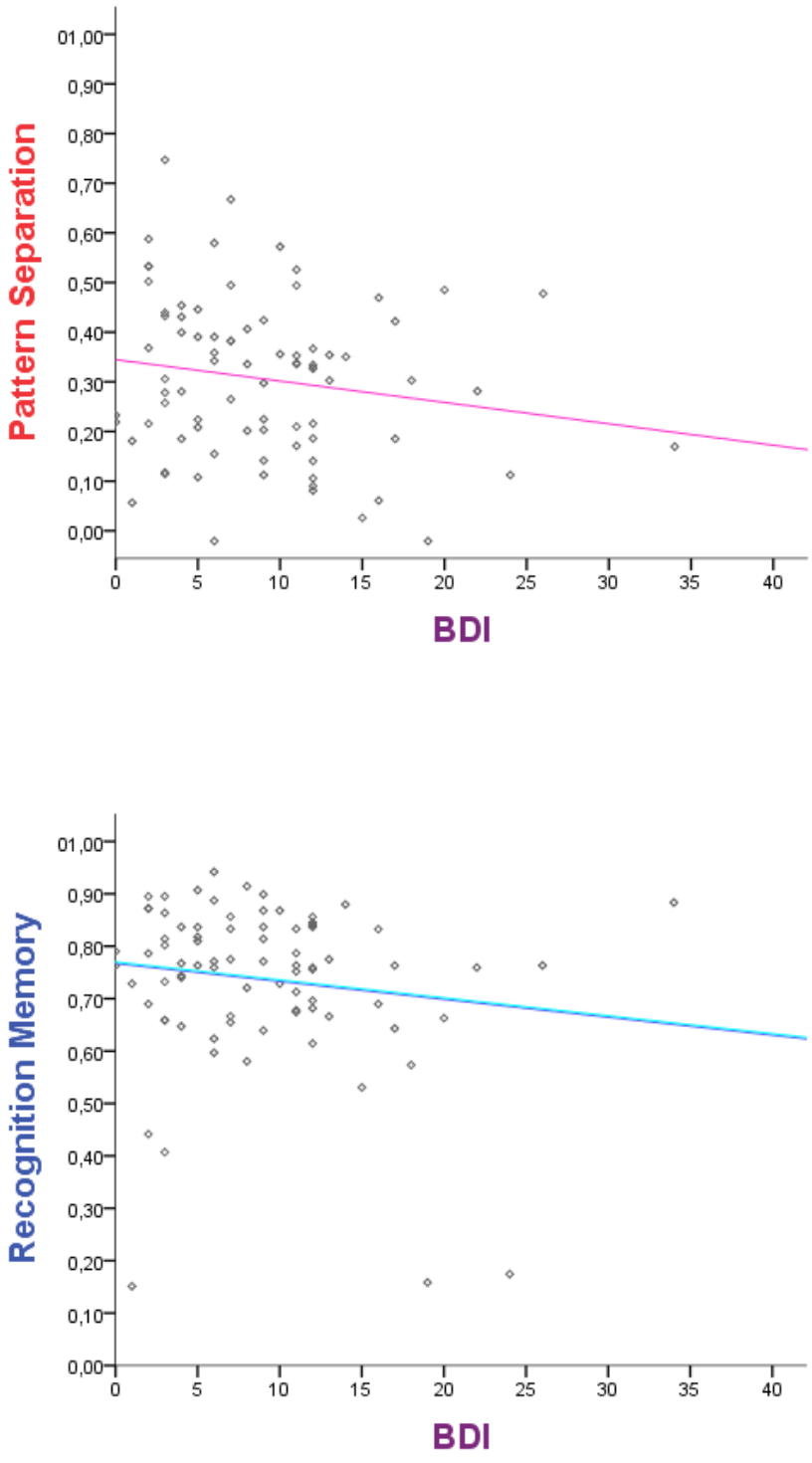

Figure 4. Pattern separation and recognition memory performance as a function of depression scores. Higher BDI (Beck's Depression Inventory) scores correlated with lower performance on the pattern separation task (r (80)= -0.14, p=0.036). Correlation BDI-recognition memory was not statistically significant.

We also used Kendall's tau-b -analysis to see if body mass index (BMI) was associated with the variables tested by the BPS-O task. Correlations BMI-pattern separation and BMI-recognition memory fell out non-significant ($r(80)=0.04$, $p=0.63$, 2-tailed and $r(80)=-0.09$, $p=0.25$, 2-tailed for the latter).

The male and female research participants were compared when it came to recognition memory and pattern separation with Mann-Whitney U Test for independent non-parametric measures. There was no difference of statistical significance between men and women regarding the recognition memory performance (Md(males)=0.76, $n=50$ and Md(females)=0.77, $n=31$, $U=657$, $z=-1.15$, $p=0.25$, 2-tailed). On the other hand, the female participants performed slightly better on the pattern separation task ($Md=0.35$, $n=50$), than the male participants ($Md=0.27$, $n=31$), $U= 571$, $z= -1.98$, $r=0.22$, $p=0.047$, 2-tailed (please see Figure 5).

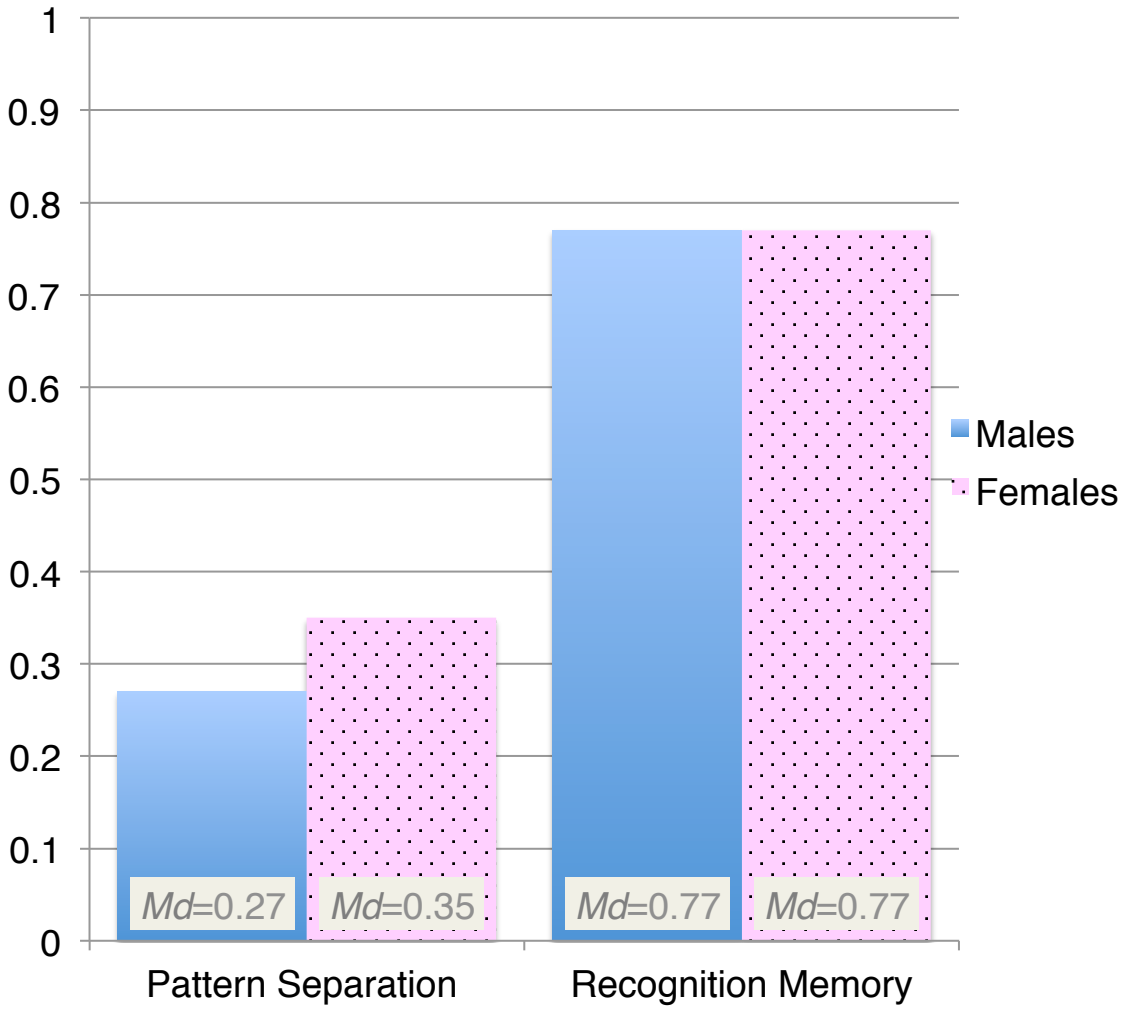

Figure 5. Gender differences in the pattern separation task. This figure illustrates the median differences in the BPS-O task. The female subjects of this study performed better than the male subjects on the pattern separation task, whilst there were no significant gender differences in recognition memory performance.

A comparison of gender groups in regards to age, BDI and BMI was conducted to see if there could be another explanation for the gender-difference we found in pattern separation. Independent t-test analysis was used for comparison of males and females in regards to BDI, since this variable was evaluated to meet the assumption of normal distribution and other parametric test assumptions. The groups did not differ in BDI scores (*M*(males)=8.46, *SD*=6.10 and *M*(females)= 9.40, *SD*=6.50; *t*(79)= -0.63, *p*=0.55, 2-tailed).

The variables age and BMI were not considered to be normally distributed, since the test of normality showed *sig.* < 0.05 for both of the variables (*sig*. 0.000 for age and *sig.* 0.008 for BMI). Mann-Whitney U test showed no significant gender-differences in age (*Md*(males)=22.0, *n*=80 and *Md*(females)=22.0, *U*=745, *z*=-0.15, *p*=0.881) or BMI (*Md*(males)=22.2, *n*=80 and *Md*(females)=21.7, *U*=664, *z*=-0.95, *p*=0.34).

Discussion

The results of this study show support for our main hypothesis. Higher scores on the depression inventory predicted poorer performance on the pattern separation task but not on the task testing recognition memory. As expected, a negative correlation was found between BDI scores and pattern separation, as measured by the cognitive pattern separation task BPS-O, and a non-significant correlation between BDI scores and recognition memory performance. These results are consistent with the two previous studies conducted by Déry et al. (2013) and Shelton & Kirwan (2013) that examined the same type of variables in relation to each other. It is important to note that the study design is correlational and thus does not prove any causal relationships.

Although we did find a clear link between depression and pattern separation, the correlation in question is quite weak as is the effect size of these results (R^2= 0.019) indicating that only 1.9 % of the variance in BDI scores is explained by the impaired pattern separation ability. This suggests that many other factors are connected to the psychopathology of depression, which is not unexpected. Results from previous studies showed slightly stronger correlations ($r(50) = -0.272$, $p = 0.05$, when lure objects were presented in the same block, ($r(50) = -0.297$, $p = 0.03$, when the lure objects were presented across blocks by Déry et al. $rs(70) = -0.245$, $p < 0.05$, by Shelton et al.) (Déry et al., 2013; Shelton & Kirwan, 2013). It is

important to note that this study had more participants than the similar previous studies. Still the statistical analysis did not find correlations as strong as those reported in previous studies. There are several external factors that may have influenced the results. During the data collection, the medical department was having important exams. This external stress may have influenced the performance and general mood of the participants. This could have been a confounding factor weakening the obtained correlation. One solution would have been to administer a valid questionnaire regarding perceived stress and to control for this factor in the statistical analysis. Another solution might have been to push the data collection to another, less stressful time period.

We also administered a questionnaire regarding different factors that could influence the results of this study, such as perceived levels of anxiety, sleeping patterns and psychotropic medication. This data could have been used for a more elaborate analysis similar to that in the Shelton et al. study (Shelton & Kirwan, 2013). Unfortunately, the data collected was highly incomplete, therefore it was reasoned that using it for this purpose would have been unreliable. The data was used only to give a descriptive perception of the study population. The questionnaire was also self-constructed and not tested in terms of internal validity. Although the face validity of this questionnaire seemed reasonable, we failed to get full answers. We reason that the questionnaire itself was hard to read. The length of the questions might have interfered with comprehension. Perhaps it could have been more desirable to use a standardized test, but at the time of completion it was not possible to find a measure that included all the variables of interest. The instruments used for assessing depression (i.e. Becks Depression Inventory) (Beck, Steer, & Carbin, 1988) and pattern separation ability (i.e. BPS-O) (Stark et al., 2013) have been properly tested before and are evaluated to lie high in terms of internal validity.

Even with a strict non-parametric test (Kendall's Tau), we obtained a significant negative correlation between depression and pattern separation. This leads us to argue that the results of this study are in line with the results of previous studies, and this study adds to the evidence of a clear link between depression and impaired pattern separation. Thus, the original purpose of this study was attained.

Aerobic exercise has been shown to facilitate pattern separation performance (Déry et al., 2013) and to lower BMI (Cuceu, Cuceu, & Dumitrescu, 2014). We wanted to see if BMI correlates with any of the variables measured by the pattern separation task. No significant correlations were found.

We also discovered some unexpected findings. A comparison of female and male research subjects' performance on the BPS-O found that female participants performed better than male participants in the pattern separation task, whilst there was no significant difference found in recognition. To see if these results were due to higher depression scores in our male participants, a comparison of the BDI scores was performed and no significant gender-differences were found. At the time of authorship, no other studies had considered gender-differences in the behavioral pattern separation task. It has been proposed that women outperform men in episodic memory tasks, even when controlling for verbal fluency (Herlitz, Nilsson, & Backman, 1997). However, this would lead to the argument that the current study should also show gender-differences in recognition memory. Female rats have been shown to have a more active hippocampal neurogenesis and faster development of hippocampus during the first weeks of postnatal development (Kalkan, Unal, Keles, & Kara, 2013). Female mice also perform better on spatial learning tasks and their hippocampus might be subject to more neuroprotective effects than the males' (Berry et al., 2012). More research has to be done in regards to gender differences in hippocampal neurogenesis and hippocampus-related

behavioral tasks in rodents (Kalkan et al., 2013). We also suggest that future studies on pattern separation in humans should study the effects of gender.

There are several factors that prevent the study from being completely representative of the general population; the relatively young age of study participants, overrepresentation of male subjects and a high affiliation to the medical study community. Nonetheless, it is positive that participants of other nationalities could be included in the study, adding to the generalizability of the findings. Previous studies (Déry et al., 2013; Shelton & Kirwan, 2013) have mainly used university students from within the USA. It is important to establish the link between depression and impaired pattern separation even in other cultures and nationalities. This is one way through which this study adds to knowledge gained in previous research.

In line with the previous two studies (Déry et al., 2013; Shelton & Kirwan, 2013) conducted on this research topic, participants were used who had not been pulled from the clinically depressed patients' pool. This can be considered both as a drawback and a positive aspect. To our knowledge there are no studies that have examined the link between pattern separation and clinically-diagnosed depression. It would be important to conduct such studies for multiple reasons. One is to be able to better compare the pattern separation abilities of the clinically depressed patients, individuals with tendencies towards depression and healthy controls. On top of the correlational analyses, Déry et al. (2013) and Shelton & Kirwan (2013) et al. used the median split technique to divide the study population into two groups based on their depression scores. The authors compared the least depressed group to the most depressed group in terms of pattern separation, recognition memory and identification of foils. Both studies found that the groups differed only in regards to pattern separation, with the high depression group preforming significantly worse. Déry et al. (2013) used Beck's Depression Inventory as a meter for depression and split the study population

into groups by a *median* of 9. The high BDI group had a *mean* of 15,68 (Déry et al., 2013), which falls under the "mild depression" category (Beck et al., 1996) . Thus, it would be extremely noteworthy to evaluate pattern separation also in individuals who suffer from moderate and severe depression and comparing those to milder forms of this condition and healthy controls. Questions which explore whether or not there will be a linear decline in pattern separation in patients with more severe depression symptoms, or if it will hit a plateau, and whether the other types of cognitive abilities tested by the behavioral pattern separation also show a decline in these more severely ill patients, should be addressed. It is also important to note that self-reported answers to questionnaires can always be exaggerated or underestimated. Thus, it would be desirable to test the association of depression and pattern separation, where the severity of depression has also been evaluated by other measures.

Yet it is clearly meaningful that both previous studies and the current study have managed to exhibit a link between high depression scores and impaired pattern separation performance. It is logical to assume that if this connection is demonstrable in a rather small, healthy population with relatively low depression scores; it might be stronger when testing a population with stronger depression symptoms. Stark et al. (2013) have suggested that the behavioral pattern separation task is a sensitive measure for discovering early memory impairment, indicating that it could possibly be used for early detection of mild cognitive disorders seen in conjunction with aging (Stark et al., 2013). Speculatively, it might be possible to detect depression tendencies in their early phase through use of the pattern separation task. More importantly as Shelton and Kirwan (2013) lifted up the possibility that hypoactive pattern separation might be specifically connected to depression, and not to other factors such as self-reported measures of anxiety, stress and poor sleep quality (Shelton & Kirwan, 2013). Using the pattern separation task on individuals at risk for depression could give the possibility of initiating some sort of early support for these individuals. Of course we

already have instruments, such as Beck's Depression Inventory, that are quite suitable for this function. Accordingly, further extensive research in human pattern separation and comparison of different tools for diagnosing depression is needed.

The results of this study cannot be directly connected to decreased hippocampal neurogenesis in individuals with higher depression scores. Even though the link between the hippocampus and pattern separation ability has been established in both rodents and humans, it is important to also investigate the relationship of depression to impaired pattern separation with the help of fMRI-studies in humans. Entirely direct measures of human hippocampal neurogenesis do not exist yet, but there are high-resolution fMRI techniques that should be explored further and used for this purpose (Yassa & Stark, 2011). Thus, study designs such as this one and those by Déry et al. (2013) and Shelton & Kirwan (2013) should also be performed whilst the brain activity pattern is investigated with the help of fMRI.

Increasing evidence that depression is linked to decreased hippocampal neurogenesis could lead to development of new, possibly more effective medical treatments. Antidepressants (Barlow & Targum, 2007; Boldrini et al., 2009; Malberg et al., 2000) and even electroconvulsive therapy (Scott, Wojtowicz, & Burnham, 2000) have been shown to increase neurogenesis. Using an approach to drug development that concentrates on neurogenesis could prove to be successful (Barlow & Targum, 2007). One other possible approach is immunological, since neuroimmunological mechanisms seem to play a role in the negative changes in neuronal plasticity associated with depression (Eyre & Baune, 2012). Additional creative approaches to development of these treatments should be explored.

In conclusion, the present study manages to elicit a previously seen link between depression and impaired pattern separation ability. This adds to the proposition that depression might be linked to decreased hippocampal neurogenesis. This relationship should be further investigated by potent fMRI-studies. Studies focusing on elaborating upon the

techniques to influence neurogenesis to treat psychiatric disorders could turn out to become groundbreaking. Full understanding of these processes is needed on both the neurobiological and behavioral level.

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Appendix

Questionnaire

Code: _____

This questionnaire is comprised of different kind of questions about your health. Please either circle the alternative that suits you best or fill in the information you are asked for. In the end of this questionnaire there is some space for your commentaries. If you want to comment on a question for example to specify your answer, please write the number of the question followed by your commentary.

Telephone number (write if you want to take part in the raffle):_____

Email address (write if you want to take part in the raffle):

_____

Nationality:_____

1. Gender: Female/ male Code:_____
2. Age:_____ years old
3. Height: _____ cm
4. Weight: _____ kg
5. Have you ever been diagnosed with depression?
   yes no
6. *Answer this question, if you answered "yes" to question number 5.*
   How many depressive episodes do you remember to have had during your lifetime?
   _____
7. *Answer this question, if you answered "yes" to question number 5.*
   Do you currently have the diagnosis "depression"?
   yes no
8. Are you on antidepressants?
   yes no
9. *Answer this question, if you answered "yes" to question number 8.*
   What is the name of your antidepressant medication (or its kind).
   _____
10. Do you take anti-anxiety medication?
    yes no
11. *Answer this, question if you answered "yes" to question number 10*
    What is the name of your anti-anxiety medication?
    _____

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12. *Answer this question, if you answered "yes" to question number 10.*
How often do you need to take your anti-anxiety medication?
nearly never 1-2 times a month 1-2 times a week 3-4 times a week nearly every day

13. Do you take medication to help you sleep?
yes no
14. *Answer this question, if you answered "yes" to question number 13.*
What is the name of your sleeping pills?
_____
15. *Answer this question, if you answered "yes" to question number 13.*
How often do you need to take sleeping pills?
nearly never 1-2 times a month 1-2 times a week 3-4 times a week nearly every day

16. Do you use any other medication for psychiatric problems?
yes no
17. *Answer this question, if you answered "yes" to question number 16.*
Please list any other psychiatric medication you take and/or what it is for.
_____
_____
_____
_____
_____

Additional commentaries:
_____
_____
_____
_____
_____

Table X

Summary of the Questionnaire Answers

Frequencies	Frequency	Valid %
Sex		
Male	50	61.7
Female	31	38.3
Missing values	1	
Field of studies / (working)		
Medicine	61	76.3
Biomedicine	6	7.5
Logopaedics	3	3.8
Economics	2	2.5
Law	2	2.5
Humanities	1	1.3
English	1	1.3
Physics	1	1.3
Psychology	1	1.3
History	1	1.3
Work	1	1.3
Missing values	2	
Nationality		
Sweden	57	82.6

Other[b]	12	17.4
Missing values	13	
Depression diagnosis		
Has been diagnosed before	6	7.4
Currently diagnosed	3	3.7
Missing values	1	
Psychotropic medication		
Antidepressant	5	6.3
Missing values	2	
Anti-anxiety	3	3.7
Missing Values	1	
Sleep	6	7.3
Other[a]	1	1.22

[a] One participant was using Lamotrigin at the time of the study.

INFORMATION FOR RESEARCH PARTICIPANTS

Request for participation
Hereby, you will be asked if you want to participate in this study that includes a computerized behavioral test and some surveys that will be answered by writing.

Background and Purpose
The general purpose of this study is to increase the understanding of the basic human cognitive functions.

The study's implementation and risks
The experiment will test your cognitive abilities in a computerized form. This means that you will be introduced to different types of stimuli on a computer screen and your answers will be stored. You will also answer some questions through surveys.

The experiment will last approximately 30 minutes.

Processing the data
Personal data from the study will be stored in a register and the data will be processed. Your information is confidential and unauthorized individuals do not have any access to the registry. When the data from the study is published, it will not be possible to identify research participants. The processing of your information is governed by the Privacy Act (SFS1998: 204). See the attached appendix with general information about the processing of personal data for research purposes at Lund University.

Privacy
The results and information relating to participants are treated confidentially.

Voluntary participation
You participation in this study is entirely voluntary and you may at any time terminate your participation without giving us any reasons.

Additional Information

In addition to this written information you will be verbally informed before the procedure. This will give you an opportunity to ask questions. You are also welcome to call any of the following people for additional information.

Mikael Johansson, Project Manager
Professor
Neuropsychological Department
Department of Psychology
Phone: 046-222 36 39

Arina Semenova, Experiment leader
Candidate
Tel: 0760534116

I have been orally informed about the study and received the written information. I am aware that my participation in this study is fully voluntary and that I, at any time and without explanation, can cancel my participation.

_____
Date of Birth

_____	_____
The participant's signature	Experiment leader's signature
_____	*Arina Semenova*
The participant's name spelled	Experiment leader's name

Mnemonic Similarity:

Set C, Set D

Part 1 – 5 minutes

Do not tell the participant that there are two phases, or that one phase tests their memory.

Steps:

1. If it's not open yet, open Matlab
2. Set directory in MatLab to the appropriate folder
3. In the command line, type: **IncidEnc(subjnum, 'dirname')** E.g. IncidEnc(999, 'Set C')
    a. Make sure your dirname matches your directory folder, otherwise it won't run
4. Make sure the cue card is in front of the screen with Indoor/Outdoor facing forward
    a. (We place cue cards in front of the keyboard reminding them of what buttons to push for what responses. V for Indoor, N for Outdoor.)
5. Read the instructions for the study phase to the subject

Instructions for Set C / Set D study phase (read this to the subject):

"First I want you to look at some pictures. When the computer program starts, it will show you pictures on the screen one by one. For each picture that you see, I want you to decide whether the item you see is an indoor item or an outdoor item. There is a little cue card below your screen to remind you what buttons to push. If you see an indoor item, I want you to press the V key on the keyboard. If you see an outdoor item, I want you to press the N key.

If you're not sure whether the item is an indoor item or an outdoor item, go ahead and take a guess, but try not to skip that trial. Also, the pictures are only on the screen for about two seconds. Try to get your responses in before the next picture comes up on the screen. The computer will not indicate whether you are right or wrong.

Do you have any questions? When you are done with this part, I'll come back into the room."

Part 2 – 8 minutes

Steps:

1. In the command line, type: **ONSTest(subjnum, 'dirname')** E.g. ONSTest(99, 'Set C')
    a. The subjnum and dirname should be the same subjnum and dirname from part 1
2. Flip cue card so that Old/Similar/New faces forward
    a. (V for Old, B for Similar, N for New)
3. Ask your participant to put on headphones and play the quicktime instructions
4. After listening to the instructions, ask if your subjects has any questions

Instructions for test phase (If the quicktime doesn't work, read this to the subject):

"This second part will be a memory test for the items you just saw. I've flipped your cue card around, so you have a different set of responses to make. The computer will show you pictures on the screen again, one at a time. This time, however, for each picture, I want you to decide whether the picture is *old, similar, or new*.

So, if you see a picture on the screen, and it is the *exact same* picture as one you saw five minutes ago, then I want you to press the V key for old, saying that's an old picture. If you see a new picture – it's new, it's different, you haven't seen it before – then I want you to press N for new. If you see a similar picture, which means, the picture comes up on the screen and you should be able to think something along the lines of, "oh, that's very similar to an old picture, *but it's not the exact same picture*," then I want you to press the B key for similar.

Do you have any questions?"