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## **RUNNING HEAD: NEUROGENESIS MAY MAKE DISTINCT CONTRIBUTIONS TO RECENT VERSUS REMOTE MEMORY IN HUMANS**

### **A role for adult hippocampal neurogenesis at multiple time scales: A study of recent and remote memory in humans**

Nicolas Déry<sup>a</sup>, Aaron Goldstein<sup>a</sup> and Suzanna Becker<sup>a\*</sup>

<sup>a</sup>Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, ON, Canada

Nicolas Déry e-mail: [deryn@mcmaster.ca](mailto:deryn@mcmaster.ca)

Aaron Goldstein e-mail: [goldsam@mcmaster.ca](mailto:goldsam@mcmaster.ca)

\*Corresponding author

Suzanna Becker, Department of Psychology, Neuroscience and Behaviour, McMaster University, PC-312, 1280 Main St. West, Hamilton, ON, L8S 4L8, Canada.

phone: 905-525-9140 ext. 23020

e-mail: [becker@mcmaster.ca](mailto:becker@mcmaster.ca)

## **ABSTRACT**

Adult hippocampal neurogenesis (AHN) is downregulated by numerous lifestyle factors including chronic stress. While the functional significance of AHN remains elusive, computational models and empirical evidence implicate immature neurons in minimizing interference between similar memories – a process termed pattern separation. The role of neurogenesis in remote memory is less clear. Some have proposed that neurogenesis promotes the clearance of old memories from the hippocampus, while others have proposed that neurogenesis promotes long-term retention of memories within the hippocampus. We used a modified version of the behavioural pattern separation task originally described by Kirwan and Stark (2007). In this task, some objects are repeated across trials, some are similar lures and the rest are novel. Participants are asked to classify each object as “old”, “new” or “similar”. The correct classification of lures as similar may tax pattern separation processes in the hippocampus and AHN. To investigate the potential role of AHN in remote memory, we introduced a two week delay between the presentation and recognition of certain stimuli. As in previous studies, we found that those with higher depression scores made significantly more errors at identifying lures as similar when presentation and recognition were separated by a brief delay. When presentation and recognition trials were separated by a longer delay, the correct classification of lures dropped to chance levels for all groups, but now lower stress and depression scores were associated with superior identification of exact repetitions. Our data suggest a role for AHN in the stabilization of remote memories.

**KEYWORDS: Episodic memory, pattern separation, consolidation, hippocampus, neurogenesis**

## 1. INTRODUCTION

Adult hippocampal neurogenesis (AHN) refers to the post-natal production of new neurons arising from stem-like cells in the subgranular zone. AHN has been found to occur in the dentate gyrus (DG) subregion in many different mammalian species (reviewed in Barker et al., 2011) including humans (Eriksson et al., 1998; Knoth et al. 2013; Spalding et al., 2013), and persists throughout life. These new cells have been implicated in some forms of learning and memory (Feng et al., 2001; Shors et al., 2001; Kempermann, 2002; Becker, 2005; Snyder et al., 2005; Aimone et al., 2006, 2009; Wiskott et al., 2006; Becker and Wojtowicz, 2007; Appleby and Wiskott, 2009; Becker et al., 2009; Weisz and Argibay 2009, 2012; Appleby et al., 2011) as well as in the regulation of emotional and stress responses (Abrous et al., 2005; Becker and Wojtowicz, 2007; Sahay and Hen, 2007; Becker et al., 2009; Snyder et al., 2011).

Newborn neurons in the DG are critical for performance on a variety of different memory tasks in rodents. For example, many groups have described the importance of AHN in distinguishing between similar contexts (Saxe et al., 2006; Winocur et al., 2006; Warner-Schmidt, Madsen and Duman, 2008; Wojtowicz et al., 2008; Hernandez-Rabaza et al., 2009; Kitamura et al., 2009; Ko et al., 2009; Guo et al., 2011; Kohman et al., 2012; Nakashiba et al., 2012). Further, a large number of tasks specifically designed to test the role of AHN in pattern separation processes implicate immature neurons in performing such a function, regardless of whether the stimuli were similar odours, visual objects, spatial locations or environments (McHugh et al., 2007; Creer et al., 2010; Guo et al., 2011; Sahay et al., 2011; Luu et al., 2012; Pan et al., 2012a; Tronel et al., 2012; Winocur et al., 2012). AHN has also been implicated in remote memory. For example, AHN is required for the long-term retention of platform location in the Morris Water Maze (MWM; Snyder et al., 2005; Deng et al., 2009; Jessberger et al., 2009)

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and the long-term persistence of memories for where an aversive shock was received (Pan et al., 2012a, 2012b, 2013). Moreover, pattern separation deficits observed in rodents lacking AHN occur across both short and long timescales. Rodents with ablated neurogenesis also display deficiencies in tasks that require cognitive flexibility (Saxe et al., 2007; Burghardt et al., 2012, Pan et al., 2012a), such as those requiring animals to forget or overcome previously learned task demands in order to respond effectively to new ones. Undoubtedly, there is a wide range of tasks that seem to require AHN. However, each of these tasks could be categorized in one of two ways: overcoming interference or memory persistence. Learning a new platform location in the MWM, learning a context-shock association in the contextual fear conditioning apparatus, and distinguishing between highly similar odour pairs, neighbouring spatial locations or highly similar visual objects all require overcoming interference. Even cognitive flexibility requires overcoming proactive interference from previously learned task demands. On other tasks that do not explicitly have a high proactive interference component, but are still shown to be deficient in those animals with ablated neurogenesis, there is generally a long time interval (>24–48h) between study and test (e.g., Snyder et al., 2005; Jessberger et al., 2009; Kitamura et al., 2009). The mere passage of time between study and test could itself be the source of retroactive interference. The more time that passes, the more opportunity there would be for encountering stimuli that could interfere with previously stored memories. On the other hand, AHN could be required for memory persistence, dictating which memories are reinforced and which memories are cleared by redistributing or adjusting the strength of connections in CA3.

Adult-born granule cells are thought to be important for pattern separation, the process of decorrelating similar inputs. Without pattern separation, less distinctive memory traces will be formed that fail to preserve the unique or novel details of an event, increasing the chance of

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memory retrieval errors. Cortical inputs project to the hippocampus primarily via the entorhinal cortex (EC). Within the hippocampus proper, output from the EC reaches the CA3 and CA1 subregions via direct perforant path projections as well as indirectly via the mossy fibre projections of the DG. The latter projections are postulated to be the predominant route by which novel incoming information is transmitted through the circuit, having a strong influence over what is encoded in CA3 (Marr, 1971; McNaughton and Morris, 1987; Treves and Rolls, 1992). In this way, information can be orthogonalized, in part because of newborn granule cells in the DG, before reaching the CA3. The associative pathways within the hippocampus, including the CA3 recurrent collaterals and the Schaffer collaterals projecting from CA3 to CA1, are postulated to perform associative retrieval, allowing the current stimulus to cue the retrieval of stored memories (Marr, 1971; McNaughton and Morris, 1987; Rolls, 2007). The process of eliciting a full memory trace from partial retrieval cues is termed pattern completion. The retrieval of stored memories that are similar to the stimulus encountered could either lead to memory enhancement or interference. For example, the retrieval of a similar memory, when recognized as being distinct from the current input, may facilitate the separate encoding of new material (Hardt, Nader and Nadel, 2013). Conversely, if the retrieved trace is not recognized as being distinct from the current input, the old trace may be modified or corrupted by details of the present stimulus via reconsolidation (Hupbach et al., 2007; Hardt et al., 2013). While this type of interference may be viewed as undesirable, pattern completion may also serve to maintain efficient retrieval by reducing pathological focusing on irrelevant details (Sahay et al., 2011; Kheirbek et al., 2012). It has been postulated that there is a trade-off between pattern separation and pattern completion (O'Reilly and McClelland, 1994). AHN may be an important mechanism that balances these two mnemonic processes.

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Neurogenesis has been implicated in memory consolidation, the process by which a memory transitions from a labile to a relatively permanent state, in two distinct ways. First, some evidence supports a role for AHN in the long-term retention of some kinds of memory, on tasks such as the MWM that are permanently hippocampal-dependent (Snyder et al., 2005; Deng et al., 2009; Jessberger et al., 2009). This suggests a role for adult-generated neurons in cellular consolidation within the hippocampus, which we will refer to as the “memory retention hypothesis”. Second, a role for adult-born granule cells has been proposed in “systems consolidation”, a process by which memories are hypothesized to become independent of the hippocampus as their traces are repeatedly strengthened in the cortex (McClelland et al., 1995; Squire and Alvarez, 1995; Maviel et al., 2004; Squire and Bayley, 2007). More specifically, it has been suggested that AHN accelerates one component of systems consolidation: the process of clearing old memories from the hippocampus (Deisseroth et al., 2004; Josselyn and Frankland, 2012; Frankland et al., 2013). This could facilitate the encoding of novel information by freeing up neural circuitry for new memory formation. In support of this “memory clearance hypothesis”, it has been reported that elevated neurogenesis accelerates systems consolidation for context-fear associations (Kitamura et al., 2009; Akers et al., 2014), a type of memory that is initially hippocampal-dependent, but can also be supported by extra-hippocampal structures. Similarly, AHN has been proposed to underlie infantile amnesia, the loss of memories acquired early in life, which is common in non-precocious neonatal species including humans and rats; the high levels of neonatal neurogenesis and continuous rewiring of the infantile brain in these species may render memories more vulnerable to interference (Josselyn and Frankland, 2012; Frankland et al., 2013). Does this mean that adults with upregulated or intact neurogenesis would perform worse on tests of remote memory as compared to those with downregulated or ablated

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neurogenesis? The answer to this question may depend on the type of memory being tested.

Some forms of memory, including allocentric spatial memory (O'Keefe and Nadel, 1978) and episodic memory (Tulving, 1983) seem to be permanently hippocampal-dependent (Vargha-Khadem et al., 1997; Mayes et al., 2001; Fortin et al., 2002; King et al., 2002; but see Rosenbaum et al., 2007). Several labs have demonstrated in rodents that AHN is required for long-term retention of spatial memories in the MWM (Snyder et al., 2005; Deng et al., 2009; Jessberger et al., 2009). In contrast, as noted above in the case of contextual fear memory, neurogenesis could facilitate systems consolidation by helping to clear memories from the hippocampus as they are consolidated in extra-hippocampal structures.

In contrast to rodent studies of neurogenesis and memory that are typically administered over a period of days to weeks, most studies that have examined the potential contribution of neurogenesis to human memory have employed tasks administered within a single experimental session. Several studies have found that lifestyle factors associated with increased or decreased AHN in rodents correlate with performance on analogous, putative neurogenesis-dependent, behavioural tasks in humans. One potentially neurogenesis-dependent task that has gained attention in recent years is the behavioural pattern separation task – object version (BPS-O), which was originally designed by Kirwan and Stark (2007) and has since evolved into numerous other versions (reviewed in Yassa and Stark, 2011). The BPS-O task includes several blocks of study and test phases. In each study phase, a set of images of everyday objects is presented one at a time. In the test phase the participant views another series of images of objects, which are either 1) identical copies (repetitions), 2) highly similar, but non-identical stimuli (lures), or 3) completely novel objects (foils). For each image, the participant is asked to judge whether the object is “old”, “new” or “similar” to one previously observed. The similar items, or lures,

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introduce a high interference component to the task. Hence, accuracy on lure trials (identifying them as “similar” as opposed to “old” or “new”) should benefit from the pattern separation function attributed to the DG (Marr, 1971; McClelland et al., 1995; Kesner, 2007) and to adult-born granule cells in particular (Becker, 2005; Aimone et al., 2006, 2009; Wiskott et al., 2006; Becker and Wojtowicz, 2007; Appleby and Wiskott, 2009; Becker et al., 2009; Appleby et al., 2011). An indirect line of evidence that behavioural pattern separation may be neurogenesis-dependent is that performance on this task is affected by several established up-regulators and down-regulators of neurogenesis. For example, following a six week-long exercise program, those exhibiting a greater change in fitness (assessed by  $VO_2peak$ ) also showed greater improvements on a visual test of pattern separation (Déry et al., 2013). On the other hand, in a healthy sample, those who scored above the median on the Beck Depression Inventory-II (BDI) demonstrated a marked deficit in correctly identifying lures as “similar” as compared to their less-depressed counterparts (Déry et al., 2013). There were no differences between groups in their ability to correctly identify repetitions or novel objects. Similarly, higher depression inventory scores as assessed by the Depression Anxiety Stress Scale were negatively correlated with behavioural pattern separation performance (Shelton and Kirwan, 2013). Another lifestyle factor associated with downregulated neurogenesis in humans is aging (Imayoshi et al., 2009; Knoth et al., 2010; Spalding et al., 2013). High-resolution fMRI and diffusion tensor imaging (DTI) studies have demonstrated that hyperactivity in the DG/CA3 region and perforant path degradation as well as mild cognitive impairment manifest with old age (MCI) (Yassa et al., 2010b, 2010c, 2011; Yassa and Stark, 2011). The same studies demonstrate a negative connection between impaired hippocampal processing and behavioural pattern separation. Thus, exercise, stress and aging, three lifestyle factors that have consistently been shown to influence



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neurogenesis in rodents, have also been shown to correlate with putative neurogenesis-dependent cognition in humans in the same manner.

To further elucidate the potential role of AHN in reducing memory interference at short versus long time scales, we sought to extend our previous findings by incorporating a long-term, remote memory aspect to our visual pattern separation task<sup>1</sup>. Thus, in addition to the traditional within-day testing that we and others have investigated, we had participants complete a visual test of pattern separation that incorporated a two week delay between the study of some targets and the subsequent testing of some repetitions and lures. Accordingly, while some participants were only presented with images of old, similar and new objects during same-day testing, others were asked to come back two weeks later for additional testing. During the two-week follow-up session, participants were presented with another set of images of everyday objects in a series of study–test phases. However, this time, some targets were originally presented on the same day, whereas other targets were from a study phase occurring two weeks earlier. We hypothesized that participants who scored high on depression and stress inventories would be impaired at identifying lures as “similar” on within-day testing, as in our previous study. At the longer time scale, the alternative theories described above make different predictions. According to the memory retention hypothesis, neurogenesis promotes long-term memory retention within the hippocampus, and thus, predictors of reduced neurogenesis such as stress and depression scores should also correlate negatively with performance across a two-week delay. Those with high

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<sup>1</sup> Pattern separation has traditionally referred to the neurocomputational process of decorrelating information that enters the DG. On the other hand, pattern separation in behavioural terms represents discriminating between highly similar stimuli. Thus, perhaps the terms ‘behavioural pattern separation’ or ‘visual pattern separation’ should no longer be used because they may be confused with the decorrelation-type processes occurring in the DG (see Santoro, 2013). However, we prefer to use the term visual pattern separation when referring to the behavioural discrimination task used here because we presume that orthogonalization in the DG is necessary for the correct identification of highly similar lure objects.

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neurogenesis levels, on the other hand, should maintain high fidelity memory representations of the studied images across the two-week delay. Alternatively, the memory clearance hypothesis predicts that those with higher neurogenesis levels should exhibit a more efficient clearance of hippocampal-dependent memories. This might be coupled with faster systems consolidation of those memories, assuming that memories of the images displayed throughout the visual pattern separation task can be supported by extra-hippocampal structures. Under this assumption, the consolidated memories of the images should be less detailed and more “schematized” (Frankland et al., 2013). Thus, one might expect relatively poor recognition of the original targets, with increased confusion between similar lures and targets studied two weeks ago relative to lures tested within the same day as target presentation.

## **2. METHODS**

All aspects of our protocol were approved by the Hamilton Integrated Research Ethics Board. Our study population consisted of healthy young adults from the McMaster University undergraduate student pool. All participants gave informed consent and were screened for the following inclusion criteria: normal or corrected to normal vision and no history or previous diagnosis of any psychiatric disorder. We excluded anyone with a long-term history of major depression because severe or multiple episodes of depression are associated with gross hippocampal pathology, including hippocampal volume loss (Campbell et al., 2004), which could overshadow any cognitive deficits more specifically related to down-regulated AHN. Chronic reductions in AHN have also been shown to compromise the cell morphology and function of other hippocampal subregions, including the CA3 (Schloesser et al., 2013). Accordingly, we only recruited participants ranging from those who did not have any signs of depression to those who were at risk for developing their first depressive episode. We recruited

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109 participants in total (age 17–27, 21 male, 88 female) and 44 returned for the second session (age 17–26, 7 male, 37 female). The data obtained from 57 of the participants have been published elsewhere (Déry et al., 2013) and re-used here, under the terms of the CC BY 3.0, in combination with data from an additional set of participants. Each participant's data was linked to a unique code and their identifying information was kept anonymous to the experimenters. However, each participant's identifying information and BDI score were forwarded to a third party for assessment. If any student was flagged as being at risk for major depression or suicide then their contact information was sent to a psychological counselor at the McMaster University Student Wellness Centre who would then contact the participant to discuss possible treatment options.

In each visit, participants completed the Beck Depression Inventory-II (BDI; Beck et al., 1996) and Cohen's Perceived Stress Scale (PSS; Cohen et al., 1983) in a private testing room. We considered the BDI to be an indicator of enduring stress as it is not overly sensitive to daily fluctuations in mood. However, the BDI score is susceptible to inflation based on a participant's current physical condition (e.g., due to illness) as it is heavily reliant on questions relating to physical symptoms such as fatigue (Moore et al., 1998). Accordingly, we also administered the PSS as a predictor of more transient stress, experienced over the past month, as its predictive value drops off after two to four weeks. It has been previously demonstrated that stress can, under some circumstances, improve hippocampal excitability, long-term potentiation and hippocampal-dependent memory (Kim and Diamond, 2002; Joëls et al., 2007; Kirby et al., 2013) as well as transiently upregulating AHN (e.g., Kirby et al., 2013). Thus, the BDI and PSS could provide not only complimentary, but also differing predictive value in terms of AHN and associated cognition. Following completion of the emotional questionnaires, each participant was

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asked to complete a new version of our visual pattern separation task that featured a delayed recognition test as well as two control tasks: a paired associates learning (PAL) task and a reverse digit span task.

We measured BDI and PSS on both day 1 and day 2. BDI and PSS scores on day 1 were used for within-day analysis. On the other hand, BDI and PSS scores from day 1 and day 2 were averaged for the day 2 “Across 2 Weeks” analysis. The average change in BDI score across day 1 and day 2 was 0 ( $SD = 4.5$ ), while the average change in PSS scores across day 1 and day 2 was  $-0.6$  ( $SD = 3.5$ ). Thus, both BDI and PSS scores were very stable across the two weeks.

The version of the visual pattern separation task used here was nearly identical to the one described by Déry et al (2013), but with one important difference. In our former study, eight blocks were presented over one day. In the current study, four blocks were presented on day 1, while the remaining four blocks were presented two weeks later on day 2. Only the first four blocks of data from the 57 participants who were analyzed previously were added to this dataset, so that day 1 data from that study would parallel day 1 data from the current study.

Each block of the visual pattern separation task had a different visual background of an outdoor scene. A single block included one study phase and one test phase, which we also refer to as a presentation phase and a recognition phase, respectively. Each presentation phase included 16 images of everyday objects that were seen for the first time. Each object was presented for 2,500 ms with a 500 ms inter-trial interval during which a white noise visual mask was displayed. Participants were instructed to focus on the visual features of each object, but were not asked to make any particular judgement about each object. Each recognition phase included a different number of images, depending on the block number. The recognition phase within the first block included 38 images in total: 8 repetitions, 8 lures and 22 unrelated foils.

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Each subsequent block included the same number of each stimulus type as in block 1, but in addition, one repetition and one lure were added from each preceding block, along with two additional foils. Following the extended two-week delay, blocks 5 through 8 (completed on day 2) contained one additional repetition and one additional lure from each block that was completed on day 1. Accordingly, there were 16 repetitions and 16 lures tested on day 2, for which identical or similar versions (respectively) had been originally presented on day 1. During each test phase the participant was explicitly asked to judge whether the image being displayed was “old”, “new” or “similar” compared to the images previously viewed. If the image was exactly the same as one previously seen, they were instructed to select “old”. If the participant did not remember seeing the image before, they were instructed to select “new”. Finally, if the participant recognized the object as being similar, but not exactly the same as one previously viewed, then they were instructed to select “similar”. A correct response is said to occur when a participant identifies a repetition as “old”, an unrelated foil as “new”, or a lure stimulus as “similar”. Correctly identifying lures as “similar” requires discriminating between two highly confusable items and thus is hypothesized to require pattern separation in the DG. On the other hand, misclassifying a lure as “old” is hypothesized to involve pattern completion processes, whereby the lure stimulus has generated a pattern of activation having sufficient overlap with that of the original target for the two objects to be considered one and the same (leading to an error in recognition). Accordingly, the correct identification of a lure stimulus constitutes a correct rejection (i.e., correctly rejecting the lure stimulus as being similar, but not identical, to the target image) whereas incorrectly classifying a lure as “old” constitutes a false positive (i.e., falsely identifying a lure as being identical to the target). Past studies have quantified how behavioural pattern separation performance varies as a function of similarity between targets and

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lures (Yassa et al., 2010a; Lacy et al., 2011; Motley and Kirwan, 2012; Déry et al., 2013; or Stark et al., 2013).

Our visual pattern separation task was constructed so that there would be a varying amount of interference between target stimuli and repetitions or lures. Repetitions and lures could be tested in the same block and context, a varying number of blocks later in a unique visual context or two weeks later in a different visual context than that in which the original study object appeared. Thus, we were able to analyze differences in traditional recognition memory (performance on repetition trials) and putative neurogenesis-dependent memory (performance on lure trials) as a function of the degree of visual and/or temporal context change between the presentation of a target and a repetition or lure. We also analyzed how performance on each of these conditions correlated with BDI and PSS scores. Importantly, the large temporal context change across the two-week delay also allowed us to assess the relation between stress and depression scores, presumably reflecting neurogenesis levels, and remote memory formation and retrieval. We considered the identification of repetitions tested two weeks after their first presentation as a measure of remote memory. Similarly, correct identification of lures when the original similar items were presented two weeks earlier would be an even more taxing measure of remote memory. Importantly, each repetition was presented three times in total (once during study, once during test and once again during a subsequent block either on the same day or two weeks later), while each lure was only presented once (albeit as three highly similar images over three different trials). Thus, each presentation of a repetition item could have been introducing non-overlapping aspects to the memory (i.e., varying visual context) in those with reduced neurogenesis, while these aspects may have been cleared in those with higher neurogenesis. At the same time, overlapping features of the memory (e.g., the repetition itself) would be the only

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aspect strengthened in those with higher levels of AHN. Therefore, we posited that participants who scored relatively high on the BDI or PSS would recognize fewer repetitions as “old” when viewed two weeks after learning by incorrectly mistaking them as similar or novel due to memory intrusions or inaccessibility of the original memory trace.

When a participant scored more than two standard deviations below the mean on low-interference foil trials on either day 1 or day 2, they were assumed to have not followed the task instructions and their data were removed from all analyses. The foil condition is the lowest interference condition and participants typically achieve near perfect scores. Nine participants were eliminated based on this criterion. Consequently, there were 100 participants left in day 1 analyses (17 male, 83 female, average age 19.5,  $SD = 2.1$ ) and 41 in day 2 (7 male, 34 female, average age 19.3,  $SD = 1.9$ ).

In order to control for differences in mnemonic discrimination on the visual pattern separation task that may have been due to factors unrelated to neurogenesis, such as deficits in executive function or working memory, we administered two control tasks. The first was a paired associate learning (PAL) task similar to the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition, Cambridge, United Kingdom) PAL task. PAL is a visuo-spatial associative learning task that is sensitive to hippocampal pathology, but was hypothesized to be neurogenesis-independent. The patterns presented in PAL lack a high interference component, having very few features in common with other patterns, and are presented at a small number of well-separated spatial locations. The second control task, reverse digit span, is a test of working memory and was also hypothesized to be neurogenesis-independent. Verbal working memory span is unimpaired in patients with medial temporal lobe lesions (Drachman and Arbit, 1966; Jenson and Squire, 2012), but requires regions of the

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auditory phonological loop including the superior temporal gyrus, anterior cingulate and fronto-insular cortex (Li et al, 2012). Moreover, Saxe et al (2007) found an improvement in working memory performance in rodents following ablation of neurogenesis, which could mean that individuals with a dysfunctional hippocampus lacking neurogenesis compensate for their memory deficit by relying on extra-hippocampal strategies, leading to superior performance on working memory and other tests of executive functions.

Since neither BDI nor PSS scores were normally distributed, we used Spearman's rho ( $r_s$ ) for all correlative analyses. Levene's test of equality of variances revealed that variability in the proportion of correct responses was equal across groups. Accordingly, for all comparisons between groups scoring in the lower and upper ranges on the BDI and PSS questionnaires we used the student's *t*-test with equal variance assumed. For repeated measures comparisons within groups we used the paired version of Student's *t*-test. We used the one-sample *t*-test to compare group performance to chance guessing (33% correct). To further test performance across delays, a repeated measures ANOVA was conducted with group (low and high BDI) as a between-subjects factor and delay (within blocks, within the same day but across blocks, and across two weeks) as a within-subjects factor. Since the cognitive data were analyzed in two different ways (task performance versus either BDI or PSS) that highly correlate with one another, we opted not to correct for multiple comparisons. For each statistical test a *p* value (two-tailed)  $\leq .05$  was considered significant.

### **3. RESULTS**

We first separately analyzed performance on the various trial types for each level of contextual change (same day same context, same day different context, and two-week delay). Overall, participants were highly accurate at correctly identifying foils as "new" (92.3%) and



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repetitions as “old” (87.6%) on the first day of testing. In contrast, participants had greater difficulty identifying lures, correctly classifying 45.5% of them as “similar”, while incorrectly categorizing 45.5% of them as “old”. Participants performed significantly worse on repetition trials when they occurred in a separate, visually-distinct block from the target item, going from 87.6% ( $SD = 8.8\%$ ) correct within blocks to 78.5% ( $SD = 23.0\%$ ) across blocks ( $t_{(99)} = 3.87, p < .001, d = 0.78$ ). On the other hand, and consistent with our previous findings (Déry et al., 2013), participants were better able to identify lures as “similar” when they were shown in a different block and within a unique visual context compared to the original target (going from 45.5% [ $SD = 17.6\%$ ] within blocks to 53.8% [ $SD = 27.8\%$ ] correct across blocks;  $t_{(99)} = 2.87, p = .005, d = 0.58$ ). At the same time, participants made significantly fewer pattern completion errors when lures were tested across blocks (as opposed to within blocks). They misclassified 45.5% ( $SD = 16.1\%$ ) of lures as “old” when they were tested in the same block as the target, but only 32.5% ( $SD = 23.1\%$ ) of lures as “old” when they were tested in a different block from the target ( $t_{(99)} = 5.54, p < .001, d = 1.11$ ).

While there were fewer “old” responses to both repeated items and lures tested across blocks, there was no change in the proportion of “old” responses to the new (unrelated foil) objects from one trial to the next. Indeed, a one-way ANOVA revealed that the proportion of “old” responses to unrelated foils remained stable across blocks ( $F_{(3,396)} = 1.21, p = .31$ ). These data suggest that there was not a general shift in strategy away from selecting “old” as a response option from one block to the next.

When lures were displayed against a visually unique background and two weeks had elapsed since the original target presentation (as opposed to being displayed on a different background, but on the same day) participants performed near chance levels at identifying lure

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stimuli as “similar”. For repetitions that were presented across a two week-long delay, participants performed about the same as they did on lure trials separated by two weeks – correctly identifying only a third of repetitions as “old”.

We next analyzed behavioural pattern separation performance as a function of self-reported depression scores (BDI) or stress scores (PSS), after correcting for response biases. From this point forward, when we refer to behavioural performance on old items we are referring to the standard recognition score (see Formula 1 below) and when we refer to behavioural performance on similar items we are referring to the pattern separation score (see Formula 2 below). If a participant was biased towards selecting the “old” response option (regardless of trial type), then their proportion of correct responses to repetition trials would be inflated. Similarly, if a participant was biased towards selecting the “similar” response option (regardless of trial type), then their proportion of correct responses to lure trials would be inflated. Accordingly, we applied the following correction formulae to repetition and lure trials, respectively:

**Formula 1.** [Standard recognition score =  $p(\text{“Old”}|\text{Target}) - p(\text{“Old”}|\text{Foil})$ ]

**Formula 2.** [Pattern separation score =  $p(\text{“Similar”}|\text{Lure}) - p(\text{“Similar”}|\text{Foil})$ ]

where  $p$  denotes the proportion of responses. Next, we divided participants into two groups based on the median BDI score. On the basis of this median split, we created a “low BDI” group ( $n = 50$ , mean BDI = 3.6, range 0–7) and a “high BDI” group ( $n = 50$ , mean BDI = 15.8, range 8–43). It is important to note that our cut-off score of 8 and above includes those who would be considered non-depressed according to the Center for Cognitive Therapy guidelines (scores of 8–10) as well as those who would fall in the mild or moderate depression category (scores of 10–18), the moderate or severe depression category (scores of 19–29) and the severe depression

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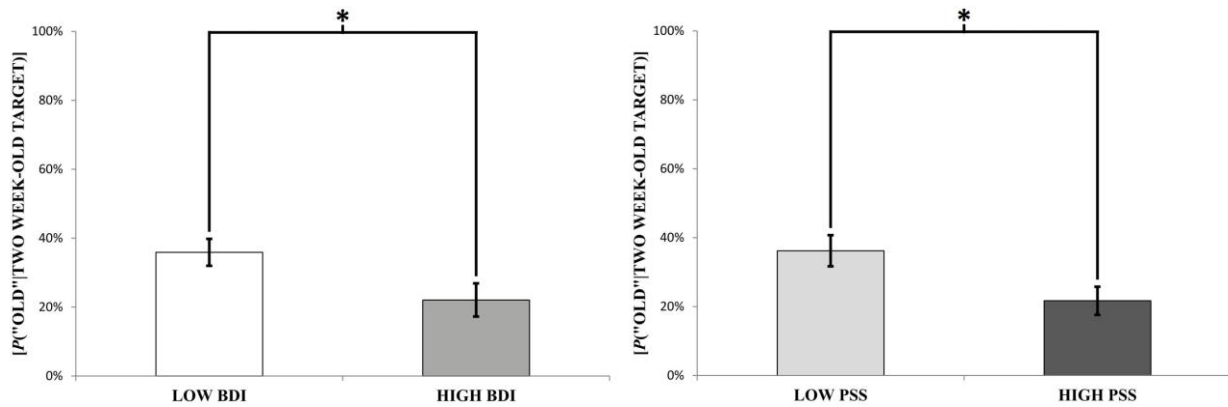
category (scores above 29). As it happens, the proportion of non-depressed participants in our sample was relatively high (65%), while those who scored in the severe depression range were relatively few (3%). Although the high proportion of non-depressed participants resulted in a lower cut-off score, a lower cut-off score would nonetheless help to maximize the number of depressed participants in the “high BDI” group, while minimizing false negatives (Beck et al., 1988). Comparable BDI scores were found in a population of 414 undergraduate students with similar age and gender demographics to our participants in a study conducted by Storch and colleagues (2004). They did not report the median, but did report a mean BDI score of 11 (SD = 8.2), which compares to our group who had a mean BDI score of 10 (SD = 8.3). Next, we performed a median split on stress scores to create a “low PSS” group ( $n = 52$ , mean PSS = 10.4, range 1–16) and a “high PSS” group ( $n = 48$ , mean PSS = 22.9, range 17–35). Low and high BDI groups had significantly different depression scores ( $t_{(98)} = 10.86$ ,  $p < .001$ ,  $d = 2.19$ ), but did not differ in age or gender. Likewise, low and high PSS groups were significantly different with respect to self-reported levels of stress ( $t_{(98)} = 14.95$ ,  $p < .001$ ,  $d = 3.02$ ), but not in terms of age or gender.

Consistent with findings in previous studies (Déry et al., 2013; Shelton and Kirwan, 2013), pattern separation scores were significantly higher in the low BDI group (42.8%) compared to the high BDI group (35.2%;  $t_{(98)} = 2.06$ ,  $p = .04$ ,  $d = 0.42$ ). Similarly, the low PSS group outperformed the high PSS group at correctly recognizing lures as “similar” when they appeared in the same block as the original target ( $t_{(98)} = 2.17$ ,  $p = .03$ ,  $d = 0.44$ ). Importantly, there were no differences between low and high BDI groups or between low and high PSS groups in standard recognition, suggesting that subjective levels of depression and stress may selectively influence pattern separation, but not recognition memory scores.

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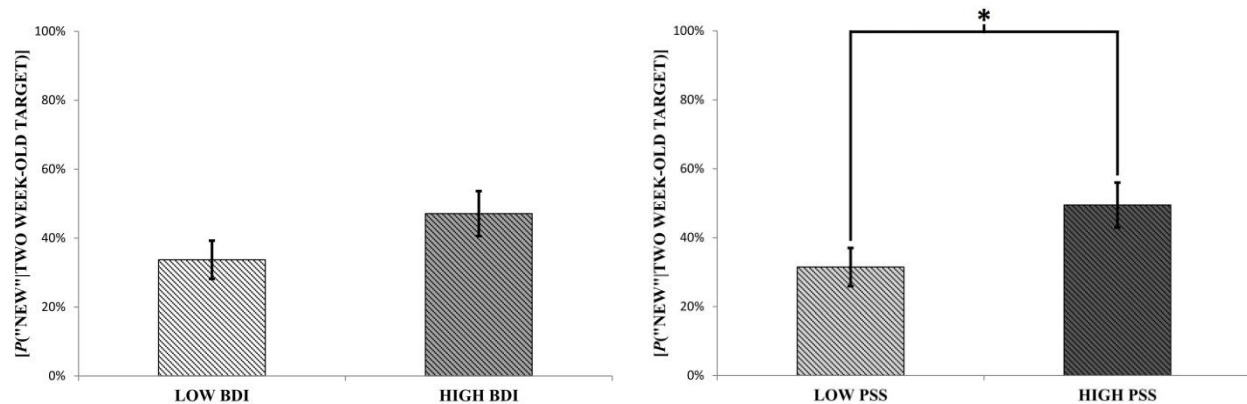
In agreement with our previous findings (Déry et al., 2013), an extended delay (on the order of minutes) and a change in visual background improved pattern separation scores for lures tested across blocks, compared to lures tested within blocks, in both low BDI and high BDI groups by 9% ( $t_{(49)} = 2.10, p = .04, d = 0.60$ ) and 13% ( $t_{(49)} = 2.76, p = .008, d = 0.79$ ), respectively. In contrast to our previous findings, there was no significant difference in lure trial performance between low and high BDI groups for those lures that were presented in a different block, but on the same day as the original targets ( $t_{(98)} = 0.89, p = .38, d = 0.18$ ). Similarly, there was no difference in across-block pattern separation scores between low and high PSS groups ( $t_{(98)} = 1.34, p = .18, d = 0.27$ ). Thus, we were unable to replicate our previous findings, where the low BDI group outperformed the high BDI group at identifying lures tested in a different block, but on the same day as the original study items (Déry et al., 2013).

Interestingly, performance on across-block lure trials correlated negatively with the number of errors in PAL. The more errors participants made in PAL, the worse they performed at correctly classifying lures as “similar”, specifically on those lures in which the original target was displayed in a previous block, but on the same day ( $r_{(98)} = -.20, p = .04, 95\% \text{ CI } [-.39, .02]$ ). In contrast, there was no significant relationship between performance on PAL and pattern separation scores when lures were tested in the same block as the original target or when they were tested two weeks later (both  $p > .50$ ). These results suggest that correctly identifying across-block lures, which follow the original study phase by an extended time period and are displayed in a unique visual context, does not require AHN (at least to the same degree as within-block lures). Rather, performance may rely on more general hippocampal contextual or associative encoding strategies that overlap with those required by PAL.



**Figure 1.** Proportion correct responses to repetitions tested two weeks after presentation. (A) Participants were split into groups based on median Beck Depression Inventory-II score. (B) Participants were split into groups based on median Cohen's Perceived Stress Scale score. \*  $p \leq .05$ .

We also examined how a two week-long delay between study and test phases affected performance at detecting lures and repetitions as a function of stress and depression scores. There was no difference between low and high BDI groups, or between low and high PSS groups at identifying lures across two weeks. However, the low BDI group significantly outperformed the high BDI group at identifying repetitions across a two week-long delay (Figure 1a;  $t_{(39)} = 2.25$ ,  $p = .03$ ,  $d = 0.72$ ). The same difference was found between low and high PSS groups (Figure 1b;  $t_{(39)} = 2.37$ ,  $p = .02$ ,  $d = 0.76$ ). Moreover, those with higher depression ( $t_{(19)} = 2.46$ ,  $p = .02$ ,  $d = 1.13$ ) and stress scores ( $t_{(19)} = 2.63$ ,  $p = .02$ ,  $d = 1.21$ ) more often classified exact repetitions as “new” as opposed to “similar”. The high BDI group incorrectly identified repetitions as “new” 47% of the time versus 34% of the time in the low BDI group (Figure 2a;  $t_{(39)} = 1.57$ ,  $p = .13$ ,  $d = 0.50$ ). The high PSS group misclassified repetitions as “new” 49% of the time versus 32% in the low PSS group (Figure 2b;  $t_{(39)} = 2.16$ ,  $p = .04$ ,  $d = 0.69$ ). Thus lower stress and depression scores are associated not only with better pattern separation scores at shorter delays as seen in previous studies (Déry et al., 2013; Shelton and Kirwan, 2013), but also with enhanced memory for repeated images of objects across longer delays.



**Figure 2.** Proportion incorrect “new” responses to repetitions tested two weeks after presentation. (A) Participants were split into groups based on median Beck Depression Inventory-II score. (B) Participants were split into groups based on median Cohen’s Perceived Stress Scale score. \*  $p \leq .05$ .

In addition to the median split-based analyses described above, we also performed correlational analyses by comparing raw BDI and PSS scores (as continuous measures of depression and stress) to our measures of interest: pattern separation and remote memory. We found a significant negative correlation between BDI scores and pattern separation scores within blocks ( $r_{s(98)} = -.21, p = .04, 95\% \text{ CI} [-.39, .00]$ ). There was also a significant negative correlation between PSS scores and pattern separation scores within blocks ( $r_{s(98)} = -.26, p = .009, 95\% \text{ CI} [-.43, -.07]$ ). Consistent with our median split analyses, these data suggest that subjective levels of depression and perceived stress adversely affect behavioural pattern separation performance at short delays.

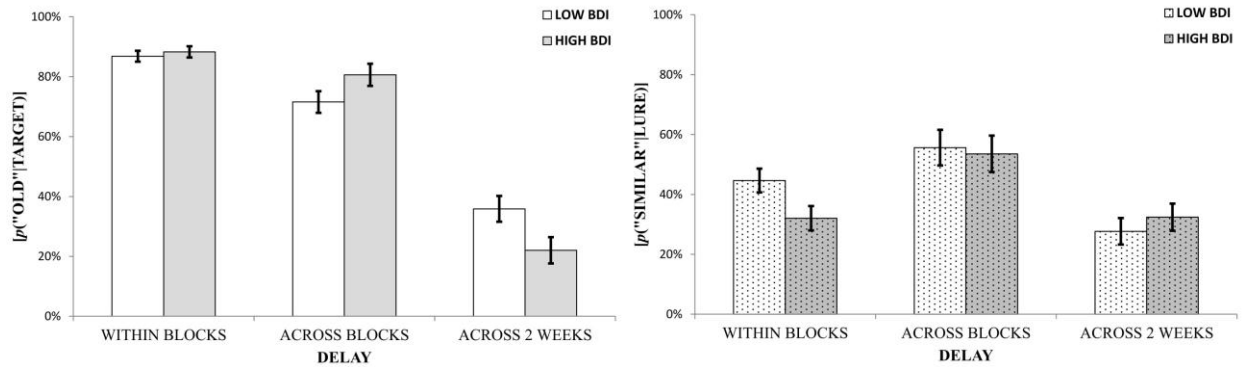
In contrast to our previous findings (Déry et al., 2013), we did not find a significant correlation between depression scores and the pattern separation scores when lures appeared in a distinct block, but on the same day as first presentations ( $r_{s(98)} = -.12, p = .28, 95\% \text{ CI} [-.31, .09]$ ). Likewise, there was no correlation between stress scores and pattern separation scores when lures were tested in the same day, but in a different block from the original target ( $r_{s(98)} = -.15, p = .15, 95\% \text{ CI} [-.33, .05]$ ).

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Not surprisingly, given the near-chance performance at identifying similar lures after a two-week delay, there was no significant correlation between BDI scores and pattern separation scores when lures were tested two weeks following the original study trials. Likewise, there was no relationship between PSS scores and pattern separation scores when there was a two week-long gap between study and test phases. We were also interested in whether stress and depression scores were predictive of remote memory performance, the ability to identify a repetition as “old” following a two-week delay. We found a significant negative correlation between BDI scores and standard recognition scores for repetitions tested two weeks following the initial study phase ( $r_{s(39)} = -.35, p = .03, 95\% \text{ CI } [-.60, -.05]$ ). Similarly, there was a significant negative correlation between stress scores and standard recognition scores for repetitions tested after a two week-long delay ( $r_{s(39)} = -.41, p = .008, 95\% \text{ CI } [-.63, -.13]$ ). Therefore, both our median split and correlational analyses indicate that the more depressed or stressed a participant is, the worse they are at recognizing exact repetitions when those objects are tested two weeks post-learning.

While the low BDI and PSS groups were not able to identify two-week old repetitions significantly better than chance, the high BDI and PSS groups performed significantly worse than chance, both averaging 22% correct compared to the 33% correct that would be expected from chance guessing (High BDI:  $t_{(19)} = 2.29, p = .03, d = 1.05$ ; High PSS:  $t_{(19)} = 2.76, p = .01, d = 1.27$ ). At the same time, only the high depression and stress groups selected significantly more “new” response options for two-week old repetitions than would have been expected from chance guessing (High BDI:  $t_{(19)} = 2.15, p = .04, d = .99$ ; High PSS:  $t_{(19)} = 2.44, p = .03, d = 1.12$ ). Together, these data suggest that, regardless of the underlying reason, those with higher levels of

stress and depression *forget* more of the original targets compared to those with relatively lower levels of stress and depression.



**Figure 3.** Plots of mean proportion correct +/- standard error, split by group (low or high BDI), for all testing timepoints. (A) Mean proportion correct on repetitions across delays (within blocks, across blocks, across weeks) (B) Mean proportion correct on lures across delays (within blocks, across blocks, across weeks).

To more specifically assess performance on the visual pattern separation task according to low and high BDI groups and across the varying delays, we employed repeated measures analyses of scores for the 41 participants who were tested on both day 1 and day 2 (after a two-week delay). A two-way repeated measures ANOVA of responses to repetitions with delay as a within-subject factor (within block, across blocks and across two weeks) and BDI group (below vs above median BDI score) as a between subjects factor revealed a significant main effect of delay ( $F_{(2,78)} = 194.21, p < .001$ ) and a significant delay by BDI group interaction ( $F_{(2,78)} = 6.85, p = .002$ ). The assumption of sphericity was not violated and the variance between groups was found to be homogenous. There was a significant decline in performance with longer delay post-learning. Participants identified more repetitions when they were tested in the same block, as opposed to a different block (but on the same day) from the original target ( $p = .001$ ). Likewise, participants were better at identifying repetitions tested in a different block, but on the same day as the study item, compared to repetitions tested in a different block and two weeks post-learning



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( $p < .001$ ). If we ignore the effect of delay, the low and high BDI groups performed similarly.

However, there was a significant delay by BDI group interaction, and if we look at the mean  $\pm$  standard error plots (Figure 3a) we see that the high BDI group had a steeper *forgetting* curve than the low BDI group.

A repeated measures two-way time (within block, across blocks, across two weeks) by BDI group ANOVA of responses to lures revealed a significant main effect of delay ( $F_{(2,78)} = 20.09, p < .001$ ), with a trending delay by BDI group interaction ( $F_{(2,78)} = 2.45, p = .09$ ). The assumption of sphericity was not violated and the variance between groups was found to be homogenous. Bonferroni-corrected post hoc tests revealed that participants were significantly better at identifying lures that were tested in a different block (but on the same day), as opposed to the same block as the original study item ( $p < .001$ ). Averaging across all delays, there was no difference in performance at identifying lures between the low BDI group and the high BDI group. There was a trending delay by BDI group interaction, and if we look at the mean  $\pm$  standard error plots (Figure 3b) we see that the interaction was driven by the shortest time delay, whereby the high BDI group outperformed the low BDI group only at the within blocks condition.

Notably, there was no difference in performance between low and high BDI groups on PAL or reverse digit span, nor did low and high stress groups differ on these measures. Moreover, there were no significant correlations between BDI scores and PAL or reverse digit span, nor were there significant correlations between PSS scores and PAL or reverse digit span tasks. These results suggest that the relative deficits on tests of pattern separation and remote recognition memory observed in those with higher stress and depression scores did not simply reflect global hippocampal processing deficits or more general cognitive impairments.

#### **4. DISCUSSION**

In the present study, we found that lower stress and depression scores predicted improved visual object recognition memory, with less false recognition of lures as repetitions on same-day tests, and greater accuracy at recognizing old items as repetitions on two-week delayed retention tests. Thus, our results provide indirect evidence from human participants that AHN is important for pattern separation across shorter delays, while strengthening memory for individual items across longer delays.

The delays chosen for the test used here were based on results from physiological and behavioural testing in rodents. There are approximately 10,000 new cells generated in the rat DG each day and about 4,000 of those cells become functional neurons (McDonald and Wojtowicz, 2005). There are approximately 1,000,000 total granule cells in the rat brain (Amaral et al., 1990). Moreover, immature granule cells that are four to six weeks old at the time of learning are preferentially recruited and thus might make more substantial contributions to learning and memory than their numbers would suggest (Kee et al., 2007). Taken together, these data suggest that a two-week delay would be sufficient for substantial neuronal turnover to take place. Kitamura and colleagues (2009) found that the dependence of memories shifts from the hippocampus to extra-hippocampal structures around three to five weeks post-learning. It has also been suggested that memories will be most affected by interference when they are several weeks old, approximately the age that it takes for them to become more dependent on extrahippocampal structures (Frankland and Bontempi, 2005). Thus, memories that are a couple of weeks old are likely to still be largely dependent on the hippocampus and might also be maximally affected by interference. At the same time, a two-week delay would not be so long

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that the original memories would no longer reside in the hippocampus and lose much of their contextual detail.

There have also been a number of behavioural studies undertaken in animals that support the timelines used here. Rats that underwent irradiation (ablating neurogenesis) exhibited a long-term retention deficit: they were impaired at recalling the hidden platform location when they were tested two or four weeks post-training (Snyder et al., 2005). Jessberger and colleagues (2009) found that animals that had neurogenesis in the DG more selectively ablated were not impaired at retrieving hippocampal-dependent memories that were one hour old, but they were impaired at retrieving those memories when tested three hours or four weeks post-learning. Finally, ERK5 icKO mice lacking neurogenesis, while not impaired in fear memory when tested one day after learning, were impaired when tested three weeks post-learning (Pan et al., 2012). These data suggest that young neurons might make functional contributions to retrieval of memories that are approximately 2-4 weeks old. Unfortunately, there are not any similar studies in humans or non-human primates in which to base our assumptions, but we tried to make a “best guess” for meaningful time points in which to test our participants based on the literature available.

On two-week delayed retention tests, regardless of stress and depression levels, all participants were at near chance levels at correctly classifying repetitions and lures, and were more likely to mistake them as being “new” rather than as “old”. It is important to note that for both the lure and repeated stimuli there was added interference between the original presentation and the subsequent test item shown two weeks later (i.e., by displaying the test objects on a different visual background as the study objects). For this reason, scores could be artificially reduced compared to a low- or non-interference condition (i.e., by displaying the test objects on

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the exact same visual background as the study objects). We cannot tell whether participants wrongly selected “new” more often for repetitions (as opposed to the equally incorrect “similar” response option) due to the test being insensitive to memories, due to participants forgetting the original study object, due to the participants’ memories being inaccessible or confused, or some combination of these possibilities. Nonetheless, the low BDI and PSS groups (hypothesized as having higher neurogenesis) are significantly better than the high BDI and PSS groups at *remembering* targets tested two weeks after their original presentation. Indeed, if the images of objects were *forgotten* we would expect participants to select the “new” response option most often for repeated items, indicating they had never seen the image before. Instead, participants usually recognized repeated items as old. Unexpectedly, similar lures viewed two weeks after the original target were most often mis-classified as “new”, suggesting that memory for the original items was either more degraded or had become more specific over time.

According to the memory clearance hypothesis (Deisseroth et al., 2004; Frankland et al, 2013), in those with higher neurogenesis levels (hypothesized here to be those with lower stress and depression scores) memories should be cleared more rapidly from the hippocampus. At the same time, those memories might be consolidated in extra-hippocampal structures in a more schematized form. If successfully consolidated and more schematized, the memories should be less detailed, and therefore more easily confused with similar incoming information, leading to inflated false memory rates for lures on the long-delay retention test relative to same-day tests. If on the other hand the memories were not consolidated, then they should simply be forgotten, resulting in worse recognition performance for both old repetitions and similar lures on the delayed retention test. The findings of the present study were not consistent with either of these predictions. We found that those with lower stress and depression scores outperformed those

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with higher scores at long-term retention of repeated items. Importantly, this was not coupled with inflated false recognition rates for lures. Instead, regardless of stress and depression levels, participants tended to misclassify similar lures as new items after a two-week delay. In fact, it was the groups who had higher stress and depression scores who more often misclassified repetitions across a two-week gap as being “new” as opposed to misclassifying them as “similar”, suggesting that their memories for the original targets were no longer accessible. Thus, in contrast to the memory clearance hypothesis, at least on the current task, it would seem that lower neurogenesis leads to enhanced forgetting.

On the other hand, according to the memory retention hypothesis, higher neurogenesis levels favor long-term retention, leading to high-fidelity, long-lasting memories for items within the hippocampus. If this is the case, on long-term retention tests, repeated items should be more accurately recognized as “old”, while lures should be more accurately recognized as “similar”, in those with higher neurogenesis levels. These predictions were only partially confirmed by the findings of the present study. Those with lower stress and depression scores, hypothesized as having higher neurogenesis, recognized more old items across a two-week gap. However, this same group was very poor at classifying lures as “similar” following a two-week delay. One reason for this could be that over time, the younger adult-generated neurons become increasingly dominated by inhibition, as they develop over a period of weeks from their young highly plastic stage to their mature, less plastic form (Wang et al., 2000; Li et al., 2012). Thus, the young neurons recruited at the time of encoding, in the course of a two-week delay, may have become less responsive, more sharply tuned, and less likely to be activated in response to similar items. Additionally, the change in internal and external context across the two-week delay may have made the lures seem much less similar to the original targets, explaining the increased likelihood

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of their being classified as “new”. By the same token, the change in context could result in repetitions seeming less similar to the identical study items. This is consistent with the finding that, over time, patterns of activity elicited by even the same stimulus are never exactly the same (Freeman and Skarda, 1985). Thus, changing visual and temporal context across two weeks might be acting to further separate highly similar items (hence the high proportion of misidentifications of lures as “new”), while at the same time making exact repetitions less similar and requiring pattern separation processes to correctly identify them as “old”.

Pattern separation and memory persistence may not be unrelated processes. According to Competitive Trace Theory (CTT), higher pattern separation in the DG would lead to reduced interference within the hippocampus, but more interference for older memories that have become dependent on extra-hippocampal structures (Yassa and Reagh, 2013). Enhanced orthogonalization of memory traces, resulting from a bias towards pattern separation as opposed to pattern completion, would result in a larger proportion of non-overlapping features incorporated into the hippocampal memory trace. In turn, the non-overlapping aspects of a previously stored memory would be more vulnerable to interference in response to a similar event. Greater levels of interference being introduced to existing memories could be one mechanism whereby older memories are altered or even cleared. At the same time, overlapping features between a new event (during encoding) and an existing memory would become strengthened. Such an account would explain why those with putatively higher rates of neurogenesis outperformed those with relatively lower rates of neurogenesis at identifying repeated items, but not lures, across two weeks. While those with lower stress and depression scores, hypothesized as having higher neurogenesis, would display superior behavioural pattern separation in the short term, there would be a higher proportion of non-overlapping information

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in the long-term memory traces for the target and the lure. On the other hand, those with higher neurogenesis would be better able to overcome the interference generated by the change in context between identical repetitions of items (e.g. background, time) and better consolidate the repeated image itself.

As overlapping aspects of a memory are reconsolidated, it has been proposed that they become more schematized in nature. Therefore, it would follow that as memories for repeated items become less precise over time, you might expect there would be more “old”-“similar” confusions rather than a transition to confusing old items as “new”. Future studies with various delays between study and test would be needed to see how incorrect selections of “similar” versus “new” on repetition trials changes over time.

AHN may enhance remote memory for repetitions in at least two other ways. First, it has been proposed that adult-generated neurons in the DG may represent the preferential storage site of memories, thus the enhanced survival of adult-born neurons would result in the enhanced preservation of memories. Indeed, while many adult-generated granule cells die off, many others persist for several months or longer and might actually endure into old age (Eriksson et al., 1998; Dayer et al., 2003; Kempermann et al., 2003). Second, the exercise-induced upregulation of AHN has been shown to accelerate the consolidation process (Kitamura et al., 2009), reducing the vulnerability of memories to intrusions by shifting their dependence into more stable hippocampal-neocortical networks rather than remaining in less stable associative networks within the hippocampus.

The question of whether remote memory deficits in those with high stress and depression scores represent an inability to form new memories, an inability to retrieve older memories or a

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deterioration of previously learned memories remains open to investigation. Importantly, stress and depression scores showed no relationship with performance at identifying novel objects or repetitions within a given test day (within or across blocks), nor did they correlate with the number of errors committed in PAL or performance on reverse digit span. Thus, differences in performance between the low and high BDI or PSS groups on our visual pattern separation task cannot be explained by generalized deficits in global hippocampal processing or by differences between groups in their working memory capacity.

In contrast to our previous results (Déry et al., 2013), we did not find a significant difference between the low and high BDI groups' ability to identify lure items that appeared on the same day but in a temporally- and visually-distinct block from the original target. There are several reasons why this might be the case. It would seem that the "high" BDI group in this study more strongly benefited from the change in context between target and lure than did the "high" BDI group in our earlier investigation (13% increase in performance versus 7%, respectively). Perhaps the change in temporal and visual context between targets and lures reduced interference to the point that discrimination of similar items no longer required AHN. Indeed, pattern separation has been reported in other hippocampal regions besides the DG. For instance, the direct pathway between EC and CA3 might further contribute to pattern separation. It has been shown that CA3 cells, in the absence of input from the mossy fibre projection from dentate granule cells, are capable of differentially encoding unique spatial locations (McNaughton et al., 1989). When neurogenesis levels are low, the sparse firing of the DG, CA3 and CA1 regions may be able to compensate by performing some degree of pattern separation, but there will be an increased susceptibility to interference due to a lack of neuronal turnover. Interestingly, in this study the ability to identify similar lures across blocks, though not correlating with depression or



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stress scores, did show a significant negative correlation with the number of errors committed in PAL, a known hippocampal-dependent task. Specifically, the more errors participants made on PAL, the worse they performed at identifying lures tested across blocks in different visual context. These data suggest that binding targets and lures to their distinct contexts may rely upon the associative pathways within the CA3 and CA1 regions, as opposed to AHN. It could also be the case that reducing the number of blocks tested in one day from eight in our previous study to four in our current study reduced memory load and thus participants were better able to remember the targets. Fewer images presented between study and test phases would reduce the total amount of interfering information experienced during the task.

We replicated our previous finding that performance at identifying lures across blocks is superior to within-block performance, likely owing to the difference in temporal and visual context (Déry et al., 2013). Together, our findings suggest that increasing the degree of change in temporal and/or visual context between the relevant study phase and lure trials allows more global (or neurogenesis-independent) hippocampal processing to assist in ‘delayed’ behavioural pattern separation performance. In contrast, when study and test phases are presented closer together in time and within the same visual context, the greater interference makes performance more dependent upon pattern separation in the DG.

Acute stress has an inverse U-shaped relationship with performance on some tasks, with moderate stress levels providing a benefit, and high stress causing impairments. Although stress has, under some circumstances, been shown to enhance hippocampus-dependent cognition and related processes such as long-term potentiation and AHN (Kim and Diamond, 2002; Joëls et al., 2007; Kirby et al., 2013), we found that subjective levels of stress at the time of testing were associated with impaired performance on putative neurogenesis-dependent recognition, with an

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increased false recognition of lures, and no benefit to traditional recognition of repeated items.

Perhaps PSS scores represent more chronic, rather than transient, levels of stress occurring over the past few days to weeks, the cumulative effects of which impair performance. Indeed, The U-shaped relationship between stress and cognitive performance that has been observed in both rodents and humans pertains to short-term levels of stress and circulating corticosteroid levels, and is even observed within the daily circadian rhythms; it appears to reflect transient ratios of occupancy of type I and II CORT receptors (for a review, see Lupien et al., 2007). As such, this so-called inverted U-shaped relationship is not directly pertinent to the present study where we are interested in longer-term effects of stress on neurogenesis levels. Neurogenesis levels are not expected to fluctuate substantially on the time course of minutes, hours or even a few days.

Moreover, newly generated neurons take 2-4 weeks to develop to the point that they are integrated within the synaptic matrix of the DG and can fire action potentials and contribute to memory formation, so a sudden change in neurogenesis levels, e.g., due to a spike in stress levels, would take several weeks to impact learning and memory. Future research could investigate more physiologically-based, objective measures of stress, such as salivary cortisol and alpha amylase, which would more accurately reflect stress levels at the time of testing. We posit that this more biologically-based measure of stress would demonstrate a stronger significant negative correlation with behavioural pattern separation performance.

Our results are broadly consistent with a long line of previous research in both human participants and rodents. Older humans, who have reduced AHN compared to younger populations (Imayoshi et al., 2009; Knoth et al., 2010; Spalding et al., 2013) exhibit deficits on a wide variety of tasks that likely require pattern separation (Toner et al., 2009; Stark et al., 2010; Yassa et al., 2011; Holden et al., 2012; Stark et al., 2013). As mentioned, our results also parallel

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those described by Déry et al (2013) and Shelton and Kirwan (2013), whereby higher scores on depression and stress inventories (the BDI and DASS) are associated with worse performance on visual pattern separation tasks. Much like the current study, the results reported in these studies are also correlational in nature since only lifestyle-based correlates of AHN were used, as opposed to any direct measurement. However, computational models have also demonstrated that when CA3 neurons receive weak input from the DG (e.g. under circumstances of reduced AHN), they will respond more preferably and rapidly to direct input from the EC (Nolan et al., 2011). Direct input from the EC would bias the hippocampal network towards pattern completion by treating stimuli as familiar, rather than novel, and engaging in associative retrieval mechanisms via recurrent collaterals (Nolan et al., 2011). In addition, evidence from rodent studies demonstrates that ablated AHN, either by genetic manipulation or by irradiation, results in severe spatial pattern separation deficits, particularly for highly similar spatial locations (Clelland et al., 2009, Guo et al., 2011; Pan et al., 2012a). On the other hand, aerobic exercise has been shown to increase AHN and leads to enhanced behavioural pattern separation performance (Creer et al., 2010; Kohman et al., 2012). Likewise, genetic upregulation of neurogenesis also improves behavioural pattern separation (Sahay et al., 2011), suggesting that the exercise-induced enhancement of behavioural pattern separation is likely due to the positive effects of exercise on AHN, rather than the more pleiotropic benefits of physical activity. Further, the persistence of remote memories for both place and context is dependent on AHN in rodents (Snyder et al., 2005; Deng et al., 2009; Jessberger et al., 2009; Kitamura et al., 2009; Inokuchi, 2011; Pan et al., 2012a, 2012b, 2013). For example, rats that underwent irradiation prior to learning demonstrated normal acquisition on the Morris Water Maze and intact retention on one-week probe trials, but a marked deficit at remembering the hidden platform location

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when tested two or four weeks post-training (Snyder et al., 2005). Despite these consistencies, our findings should nonetheless be considered preliminary because depression and stress scores cannot be considered as accurate predictors of AHN. Further, our results are inherently noisy. However, it should be noted that remote memory performance in rats varied widely depending on the level of neurogenesis. For instance, Jessberger et al (2009) found that a slight (15%) depletion of hippocampal neurogenesis had no effect on recognition memory when tested three hours and one month post-training, whereas a higher degree of neurogenesis knockdown (85%) impaired memory retrieval on delayed retention tests. Thus, it would be expected that neurogenesis-dependent cognition in humans would demonstrate marked variability depending on the always fluctuating levels of AHN (due to influence from any combination of neurogenesis regulators). In addition, a non-invasive direct method for assaying AHN in humans remains to be discovered. At present, lifestyle-based correlates of AHN that have been reliably shown to regulate neurogenesis in immunohistochemical studies in rodents may offer the best opportunity to estimate rates of granule cell production and/or survival in humans. We are currently exploring various physiological correlates that may provide improved predictive value compared to the subjective self-report questionnaires used here.

Future studies should be aimed at further investigating the hypothesis that AHN controls the level of pattern separation versus pattern completion in the DG, which may in turn contribute to the amount of overlapping versus non-overlapping information being coded or cleared in the hippocampus, respectively. One way to test this hypothesis in humans would be to develop a protocol similar to the one used here, except with many more trials occurring over a period of weeks to months. A limitation of the current study was the limited number of similar and

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repeated objects tested across the two-week delay, which precluded analysis of the relationship between degree of lure similarity and accuracy at correctly identifying them as “similar”.

If those with putatively higher rates of AHN (based on a variety of neurogenesis regulating lifestyle factors) are better at recognizing repetitions that were presented multiple times, among distractor items and in multiple different contexts, then it would lend further support for the idea that AHN is important for maintaining remote memories that are subject to interference. Increasing the frequency of learning trials over successive days or weeks might also rescue performance in those with downregulated neurogenesis by increasing the opportunity for repeated items to be strengthened in memory and maintaining appropriate object-cue associations, thereby reducing the impact of a changing external environment on object recognition. Accordingly, the number of trials that participants are asked to complete may also affect the contrast in performance between those with putatively low versus high levels of AHN. Such a study might elucidate a set of specific strategies that could be used to overcome deficits in long-term memory formation or retention in those with reduced neurogenesis and thus pattern separation. Interventions targeted at upregulating neurogenesis could also be used to improve behavioural pattern separation and remote memory performance. Indeed, we have previously demonstrated in sedentary but otherwise healthy young adults that taking part in a long-term aerobic exercise regime is sufficient to reverse the behavioural pattern separation deficits in those who had marginally lower fitness (assessed by  $VO_{2peak}$ ) and marginally worse performance on a visual pattern separation task prior to starting a long-term exercise program (Déry et al., 2013). Thus, exercise may be one intervention that can be used to prevent the decline in behavioural pattern separation performance as humans age, as well as in younger

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adults who may also be at risk for downregulated AHN, such as those with stress-related psychiatric disorders.

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