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Research Report

Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: Effects of interference, stress and depression

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ABSTRACT

Prolonged stress causes dysregulation in the hypothalamic-pituitary-adrenal axis and may contribute to the pathogenesis of major depressive disorder (MDD). MDD is associated with pathological changes in several brain regions, particularly the prefrontal cortex and hippocampus. Evidence from animal research suggests that one of the earliest signs of pathological change after exposure to stress is a reduction in hippocampal neurogenesis. We therefore sought to test the prediction that people in the earliest stages of a first episode of depression would show selective memory deficits on neurogenesis-dependent tasks. Our computational model predicts that new neurons are important for representing distinct contexts; thus, when overlapping memories are learned over an interval of several days, during which time some neuronal turnover has taken place, the neurogenesis should reduce the potential for interference between the overlapping memories. At much shorter time scales, within the span of a single memory episode, rather than contributing to pattern separation, neurogenesis might play more of an integrative role in mediating contextual associative learning. Consistent with this, empirical evidence from animal studies suggests a role for the new neurons in forming complex event memories that bridge across time delays. This leads us to predict selective memory deficits on putative neurogenesis-dependent tasks in the earliest *pre-clinical* stages of a first episode of depression, before a clinical diagnosis has been made and prior to the development of more serious pathological brain changes. We present the results of new simulations with the model, lending further support to the prediction that neurogenesis reduces interference when memory events are separated by several days. We also report findings from an empirical study in which we tested a large number of undergraduates on a set of cognitive and memory tests from the CANTAB battery, and also administered neuropsychological inventories for stress, depression and anxiety. One of the subtests in the CANTAB battery, the delayed match to sample (DMS) task, was of particular interest as delayed non-match to sample has been

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found in animal studies to be dependent upon neurogenesis. Our empirical results indicate that as predicted, participants scoring high on the Beck Depression Inventory show a selective deficit on the DMS at long delays while performing on par with non-depressed participants on all other tasks. The potential to detect very early signs of major depression using simple neurogenesis-dependent cognitive tests could have important implications for the diagnosis and treatment of this debilitating and highly prevalent disorder.

1. Introduction

The hippocampus is a part of the brain crucial to some forms of memory. It is relatively well preserved across the evolutionary scale in mammalian species, with homologous structures seen in birds and even in reptiles. In humans, this region of the brain is crucial for supporting certain kinds of memory, namely, memory for complex associations and specific events or episodes. In general, this type of memory system has been characterized as forming "conjunctive codes" for complex associations (see e.g. McClelland, McNaughton and O'Reilly, 1995). A conjunctive, associative memory system is crucial for remembering specific episodes, such as where one parked the car on a given morning, in spite of having parked the car in the same lot, in similar contexts, on numerous other occasions. Theoretical neuroscientists have for many years puzzled over what it is about the hippocampus that places it in this privileged position of supporting episodic memory formation. One intriguing aspect of hippocampal function is the fact that the dentate gyrus region of the hippocampus exhibits neurogenesis, the generation of new neurons, throughout the lifespan. It has been over four decades since the ground-breaking discovery of adult hippocampal neurogenesis (Altman and Das, 1965), a phenomenon that has been established in a wide range of species, including humans (Eriksson et al., 1998; Manganas et al., 2007; Pereira et al., 2007). In the dentate gyrus of the young adult rat hippocampus, for example, there are about 1,000,000 granule cells, and about 10,000 new neurons are generated per day, of which about 40% survive to maturation (McDonald and Wojtowicz, 2005). The dentate gyrus is critically situated within the so-called trisynaptic circuit in the hippocampus (see Fig. 1), so that information flows from the rest of the brain, via the entorhinal cortex (EC), through the dentate gyrus and CA3/CA1 subregions. On the other hand, there are also short-circuit connections from the EC to the CA3/CA1 by-passing the dentate gyrus. Thus not all forms of learning and memory may be dependent upon the dentate gyrus, and hence dependent upon neurogenesis. Indeed, empirical evidence from studies using selective ablation and/or genetic manipulation of the dentate gyrus supports a role for the this structure, and hence for the entire trisynaptic circuit, in rapid learning of novel contexts (Nakashiba et al., 2008) and in maintaining distinct representations of similar events such as nearby spatial representations (Gilbert, Kesner and Lee, 2001), while the short-circuit pathways by-passing the dentate gyrus are sufficient to support paired associates learning and incremental spatial learning (Nakashiba et al., 2008; Gilbert and Kesner, 2003). Thus, the role of neurogenesis is most likely tied to the dentate-gyrus specific learning and memory functions.

1.1. *Computational theories of hippocampal function*

Several related theories have been proposed to describe the role of new hippocampal neurons in learning and memory. Based on evidence that neurogenesis peaks in early adulthood and declines throughout life, Kempermann (2002, 2008) suggested that the gradual addition of new neurons into the existing network of the dentate gyrus could allow the hippocampus to deal with novelty and the concomitant evolution of cortical representations, by maintaining a high degree of plasticity throughout the lifespan. Nottebohm (2002) suggested that the newly born neurons may be recruited preferentially for storing new memories, thereby protecting old memories from interference. Consistent with this hypothesis, Wiskott, Rasch and Kempermann (2006) demonstrated in a simple neural network model that the addition of highly plastic new neurons does effectively prevent new learning from interfering catastrophically with older memories. Conversely, Feng et al. (2001) proposed that neurogenesis is important for clearing out older memories once they are consolidated, and several modelers have demonstrated in abstract neural network models that neuronal turnover improves acquisition by helping to discard older memories (Chambers et al., 2004; Crick and Miranker, 2006; Deisseroth et al., 2004). Becker (2005) proposed a computational model of hippocampal coding incorporating neurogenesis, as shown in Fig. 1. The model attributes a unique role to the hippocampal region in encoding of complex associations, explaining its importance for episodic memory. Moreover, the constant neural turnover in the dentate region ensures that each new event is encoded uniquely, without interfering with previously or subsequently stored memories. The associational pathways in the CA3 and CA1 regions of the hippocampus can then integrate this novel experience with prior learning episodes, and perform associative retrieval. Thus, the new neurons support a gradual change in the internal representation within the dentate region, so that an event such as where one parked the car on a given day will be encoded distinctly from a highly similar event such as where one parked the car in the same lot on the previous day. This postulated role for new neurons in supporting a gradually evolving representation of context could have important implications for learning at a variety of time scales. At short time scales, the new neurons that may be active within a given episode would not be expected to have changed much. Hence, the common pool of neurons active across the duration of an episode within a given context may help to link the elements of an episode together, by providing a common "contextual glue". Our study of human performance on the delayed match to sample task addresses the putative role of neurogenesis at this short time scale. On the other

hand, at longer time scales, the neuronal turnover could have the opposite effect: as the pool of new neurons available on a given day would differ greatly from that available many days later, rather than gluing elements together via a shared neuronal representation, the new neurons could contribute to highly distinctive representations for events separated by multiple days. Thus, when the same stimulus is encountered at two different times separated by a long delay, the neuronal turnover may result in very distinctive representations of the two contexts. An important empirical prediction from this model is that animals lacking neurogenesis should have particular difficulty on learning and memory tasks where there is the potential for high interference, when similar material must be learned at different times; this is a topic that we will return to in the Simulation 1 section.

1.2. *Empirical studies of animals with reduced neurogenesis*

Evidence from the studies of animals treated with irradiation or anti-mitotic agents to reduce neurogenesis has shed further light on the functional role of the new neurons. The evidence to date indicates that the new neurons are critical for some,

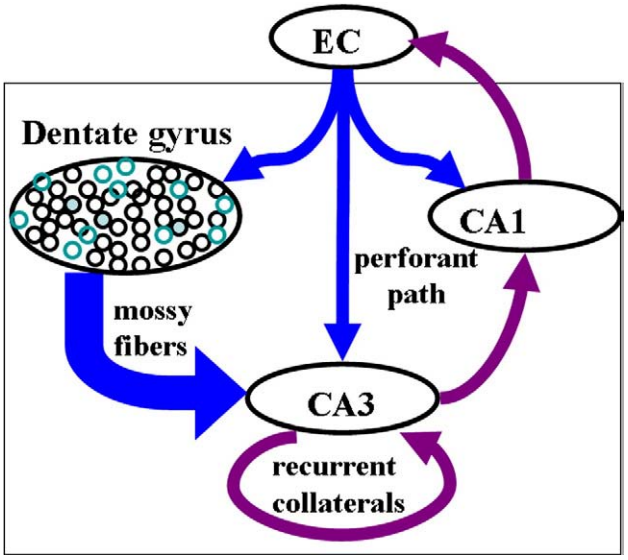

Fig. 1 – The major subregions and connections within the hippocampus. Most of the communication with the rest of the brain occurs via reciprocal connections with the entorhinal cortex (EC). Input pathways are shown with blue arrows; feedback pathways are shown with purple arrows. The hippocampus, via its extensive connections with many brain regions, is optimally positioned for both encoding and recall of complex associations. The EC in turn projects via the trisynaptic circuit through the dentate gyrus, CA3 and CA1 subregions and then back to the EC. There are also more direct pathways within the hippocampus from the EC to the CA3/CA1, bypassing the dentate gyrus. The dentate gyrus is neurogenic through the lifespan, and is therefore well positioned to influence coding throughout the hippocampus, by contributing a distinct neural encoding of context that constantly evolves over time, as new neurons constantly mature and become active.

but not all, hippocampal-dependent tasks. For example, spatial learning in the Morris water maze is disrupted by hippocampal lesions (Morris et al., 1990) but not by irradiation (Snyder et al. 2005; Wojtowicz et al., 2008). While irradiated animals learn the water maze at a normal rate, their long-term memory retention of the hidden platform location is greatly impaired relative to controls when they are re-tested four or more weeks later (Snyder et al., 2005). This finding is consistent with predictions of our computational model (Becker and Wojtowicz, 2004; Becker, 2005) that the new neurons are important for protecting older memories against interference. In addition to their contribution to distinct encoding of events, the new neurons seem to be critical for linking events across time when they are part of the same context. Many modelers have postulated computational roles for the hippocampus in linking stimuli across time delays and/or linking stimuli with background contextual cues (e.g. Grossberg and Merrill, 1996; Wallenstein, Hasselmo and Eichenbaum, 1998; Doboli et al., 2000; Burgess et al., 2001; Rudy and O'Reilly, 2001; Gluck and Myers, 2004; Rodriguez and Levy, 2004). Interestingly, a growing body of empirical evidence suggests that dentate neurogenesis, in particular, is critical for these functions. Thus, animals lacking new hippocampal neurons show deficits on trace conditioning (Shors et al., 2001), contextual fear conditioning and delayed non-match to sample (DNMS) at long delays (Winocur et al., 2006; Wojtowicz et al., 2008), while performing normally on corresponding non-hippocampal control tasks, delay conditioning (Shors et al., 2001), cued fear conditioning and DNMS at short delays (Winocur et al., 2006), respectively. Moreover, voluntary running enhances neurogenesis in rodents (van Praag et al., 1999) and correlates weakly with improved performance on contextual fear conditioning (Wojtowicz et al., 2008). Based on these data, it has been proposed that the new neurons contribute a gradually evolving representation of spatio-temporal context (e.g. Aimone et al. 2006; Becker and Wojtowicz, 2007; Wojtowicz et al., 2008) that links together the components of an episode across modalities, across space and across time.

1.3. *Link between stress, depression and neurogenesis*

Animal studies and computational models have led to several important empirical predictions regarding the role of neurogenesis for human memory. Specifically, our computational model predicts that reduced neurogenesis should be associated with increased interference in learning/retrieving memories of similar items. Empirical data also predict a critical role for new neurons in tasks such as delayed match to sample at long delays and contextual fear conditioning. In the absence of a direct means of assessing neurogenesis in human participants, we consider populations who are likely to have suppressed neurogenesis, based on empirical findings from animal studies. Several environmental and lifestyle factors affect neurogenesis. These include stress-related reduction in neurogenesis (e.g. Gould et al., 1998; McEwen and Magarinos, 2001), and exercise and environmental enrichment-related increases in neurogenesis (van Praag et al., 1999; Nilsson et al., 1999; Olson et al., 2006; Pereira et al., 2007). We are particularly interested in the effects of stress on neurogenesis because

stress is an important factor contributing to the pathogenesis of major depressive disorder (MDD). People in a first episode of depression do not exhibit detectable hippocampal volume loss (Campbell et al. 2004), but might exhibit reduced neurogenesis, as animal studies show that even relatively brief (e.g. several days) exposure to severe stress is sufficient to cause a neurogenesis reduction (McEwen and Magarinos, 2001). Moreover, it is possible that restoration of neurogenesis may be critical to recovery from depression. We hypothesize that the neural turnover in the dentate gyrus helps the hippocampus in encoding context, and making use of these contextually bound representations in generating context-appropriate emotional behavior and responses, as illustrated in Fig. 2. This could explain the mounting evidence for a critical role of the hippocampus, and more specifically, neurogenesis, in recovery from depression; for further discussion, see Becker and Wojtowicz (2007) and the General discussion and conclusion section.

In summary, we predict two important functions of hippocampal neurogenesis, namely, (1) to create distinct representations of similar events, thereby minimizing interference between highly similar memories and between memories acquired at different periods of time, and (2) to create a gradually evolving representation of spatial, temporal and other contextual cues that serves to bind together elements of a memory into coherent episodic memory traces. In Simulation 1, using a previously published computational model, we further test the prediction that neurogenesis reduces interference. In Experiment 1, we test the prediction that individuals who score high on measures of stress and depression, and may therefore be vulnerable to a depressive episode, will exhibit selective deficits on neurogenesis-dependent forms of learning and memory.

2. Simulation 1

We have developed a computational model of the hippocampal memory circuit that incorporates neurogenesis in the dentate gyrus (Becker, 2005). The model incorporates novel learning rules for hippocampal coding, based on the optimization of a global cost function, locally approximated by simple Hebb-like learning rules. The learning equations implement a form of simple Hebbian learning in the perforant path (EC-to-dentate gyrus, EC-to-CA3 and EC-to-CA1 connections), heteroassociative Hebbian learning in the CA3-to-CA1 connections and temporal associative learning in the CA3 recurrent collaterals. The model is built upon several key assumptions regarding hippocampal coding: (1) there is sparse coding (low activity levels) in all regions; (2) the projection pathway from the DG to CA3 (mossy fiber pathway) is strong (very high synaptic strengths) and sparse (very low probability of connectivity); (3) the CA3 pyramidals are highly interconnected via recurrent collaterals; (4) the trisynaptic pathway involving the dentate gyrus participates in encoding, not recall; and (5) the CA3 collaterals are active during recall but not encoding. Note that assumptions 1–3 are supported by a large body of empirical evidence and are common to many computational models (for a review, see Becker, 2005); although assumptions 4–5 are more controversial, they are also well supported empirically, and have been incorporated into several previous models (e.g. Treves and Rolls, 1992; Hasselmo, Schnell and Barkai, 1995; Hasselmo and Wyble, 1997). Thus, in the model, granule cells in the dentate gyrus (DG) are active during encoding and send a powerful, sparse, driving input to the CA3 region, but they are inactive during retrieval. Our model predicts a role for neurogenesis in minimizing interference by generating distinctive codes for similar items. Here, we investigate the role of neurogenesis in the retention of long-term memories after delays of several weeks.

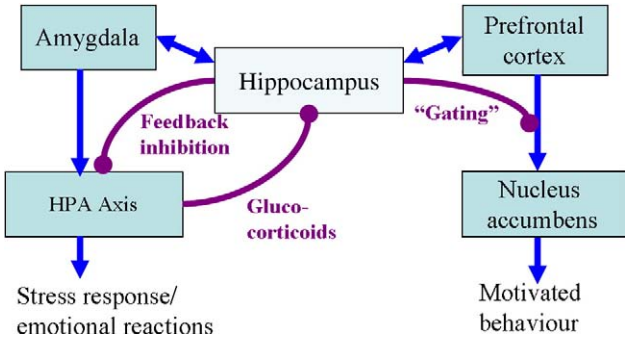

Fig. 2 – The hippocampus modulates motivational, emotional and stress-related responses via inhibitory feedback control over the hypothalamic-pituitary-adrenal (HPA) axis, and via gating the flow of information in motivational pathways from the prefrontal cortex to nucleus accumbens (for a review, see Becker and Wojtowicz, 2007).

2.1. *Methods*

We simulated the effect of preventing neurogenesis in a paired associate learning task. Each model was trained on a set of 10 paired associates consisting of randomly generated patterns on Day 1, followed by a simulated retention interval of 4 weeks, and then a final cued recall test of the original paired associates. During the retention interval, new unrelated items are learned, a potential source of interference with the original paired associates. Each of the models simulated had the following architecture: 200 input (EC) neurons, 1000 dentate gyrus neurons, 300 CA3 neurons and 400 CA1 neurons. Activity levels and other architectural constraints and learning rate parameters were as described by Becker (2005). Twenty repetitions of each model were run, to generate results of 20 simulated "subjects". Three different versions of the model were compared: (1) no neuronal turnover; (2) neural turnover and no preferential bias toward new neurons during encoding; i.e. every neuron in the dentate layer has an equal chance of becoming active when a novel pattern is to be encoded; (3) a model with neural turnover and preferential recruitment of new neurons for new memory formation; that is, new neurons were more likely to be selected for activation when a new memory was to be stored. Each model was first trained on a set of paired associates, and then on subsequent weeks, the passage of time and consequent decay of old memories was simulated by exposing the model to a set of random, unrelated items. On each week, the model was then tested for retention of the original set of paired associates. For each of the three models, the rate of neuronal turnover was

varied from 2% to 50% per week during the retention interval of the simulated experiment.

2.2. Results

The elimination of neural turnover in the model resulted in a much steeper forgetting curve during the retention interval. At the highest levels of neuronal turnover, retention improved but the "preferential recruitment" effect was negligible. At lower levels of turnover (2%) (shown in Fig. 3), preferential recruitment was important in allowing the network to take advantage of the relatively small numbers of new neurons.

2.3. Discussion

The simulated result of a neurogenesis-mediated protection of older memories from interference by subsequently acquired memories is consistent with the data from Synder et al. (2005), on the Morris water maze task. Snyder et al. used irradiation to prevent survival of newly generated neurons. Rats irradiated prior to learning in the Morris water maze displayed normal acquisition curves, progressively improving on probe trials at locating the hidden platform. In contrast, on the 2 week and 4 week probe trials, irradiated rats exhibited long-term retention deficits, performing significantly worse than controls.

3. Experiment 1: Correlation between stress, depression and memory test performance

It is of interest to test human participants who are likely to have reduced neurogenesis on the same tasks as simulated in our computational model. We would predict that people with reduced neurogenesis have difficulty retaining hippocampal-dependent memories over long periods of time, in the range of weeks to months. Such studies are hampered by the lack of a direct means of assessing neurogenesis non-invasively in humans. One could test populations such as highly stressed and depressed individuals who are likely to have reduced neurogenesis. However, a complicating issue, given the longitudinal nature of such studies, is that neurogenesis may fluctuate over time, along with stress and depression levels and numerous other lifestyle correlates. Furthermore, it is unethical to maintain people with syndromal levels of depression in an untreated state for an extended period of time. We therefore decided to focus on tasks that can be completed in a single session in our initial studies of depressed populations. Experiment 1, described next, reports the results of such a study.

3.1. Methods

The protocol for this study was approved by the McMaster Research Ethics Review Board (MREB). Participants were McMaster University undergraduates who had normal or corrected-to-normal vision and who had never been diagnosed with or treated for any psychiatric disorder. Participants received either ten dollars or course credit as compensation. Data were collected from 156 participants over a 2 year period. Participants first completed computerized versions of the Beck Depression Inventory (BDI) Beck Anxiety Inventory (BAI) (both licensed from Psychological Corp.), and Cohen's Perceived Stress Scale (PSS) (freely available at http://www.psy.cmu.edu/~scohen/scales.html), and then a series of subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (licensed from Cambridge Cognition Ltd.). The BDI consists of 21 multiple choice questions about the individual's mood during the past week, using a 4-point scale from 0 to 3. The BAI, similar to the BDI, consists of 21 multiple-choice questions that ask participants to rate various measures of their anxiety levels within the past week, on a 4-point scale. The PSS consists of 10 multiple-choice questions that ask participants to rate various measures of their perceived stress level within the past month, on a 5-point scale. Descriptions of the CANTAB tests used in the present study are provided in Table 1. The tests employed in the present study included a familiarization task (Motor Screening), four memory tests (Delayed Matching to Sample, Pattern Recognition Memory, Spatial Recognition Memory and Paired Associates Learning) and an attention test (Rapid Visual Information Processing (RVP)). Testing was carried out in a small quiet testing room free of windows or other visual distractions, using a laptop computer with a 14 inch screen and touch-screen interface. Participants completed computerized versions of the BDI, BAI and PSS using a touch-screen to select their responses to the multiple choice questions. Participants responded using a button-box for the RVP CANTAB test, and using the touch-screen for all other CANTAB tests.

Data for each participant were stored anonymously, coded by the participant's ID number. Additionally, as required by

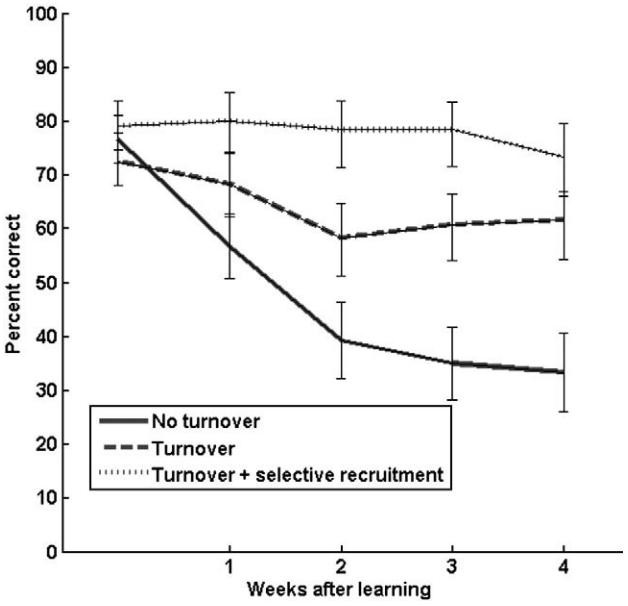

Fig. 3 – Effects of neurogenesis on the percentage correctly recalled paired associates across a simulated retention interval of 4 weeks. Top curve: model performance with no neuronal neurogenesis. Middle and bottom curves: performance of models in which 2% of neurons per simulated week are randomly replaced during the retention interval. Bottom curve: in addition to neurogenesis, the new neurons are given a bias so that they are more likely to be activated relative to older neurons.

Table 1 – CANTAB tests used in the present study.

Test	Assessment of	Description of test
Motor screening	Task familiarity: ability to master touch-screen interface and follow basic task instructions	Participants touch the flashing cross, which appears sequentially in different locations on the screen.
Delayed matching to sample	Memory: forced choice recognition for visual patterns	The participant is shown a sequence of visual stimuli and must study each stimulus and then select it from one of four sample stimuli presented after a delay of 0 to 16 s. Each stimulus consists of a rectangular complex pattern composed of four different irregularly shaped and colored subcomponents.
Paired associates learning	Memory: episodic memory and learning for object-place associations	The task alternates between study and test trials. In a study trial, six white boxes are displayed on the screen and are opened in a randomised order, with one or more of the boxes containing a pattern. In a test trial, the patterns are then displayed in the middle of the screen, one at a time, surrounded by the six white boxes; the participant must select the box where the pattern was originally located. If an error is made, the patterns are re-presented to remind the participant of their locations. The difficulty level (number of patterns within the boxes on a given study trial) increases through the test.
Pattern recognition memory	Memory: forced choice recognition for visual patterns	The test alternates between study and test phases. During each study phase, 12 novel visual patterns appear, one at a time. During each test phase, in a series of two-alternative forced choice tests, two patterns appear simultaneously, and the participant selects the one that is recognized.
Spatial Recognition Memory	Memory: forced-choice recognition for spatial locations	The test alternates between study and test phases. During each study phase a small white square appears sequentially at five different locations. During each test phase, in a series of two-alternative forced choice tests, two squares appear simultaneously and the participant selects the recognized location.
Rapid visual information processing	Sustained attention	A white box appears in the center of the computer screen, inside of which digits, from 2 to 9, appear one at a time in a pseudo-random order, at the rate of 100 digits per minute. Participants must detect target sequences of three consecutively presented digits (e.g. 2-4-6, 3-5-7 or 4-6-8).

MREB, each participant's BDI results, together with their name and phone number, were made available to a clinical Psychologist at the McMaster Centre for Student Development (CSD), who could refer them for counseling, if warranted, based on their responses on the BDI. Participants were scored as depressed if their BDI score was in the "severely depressed range", a score totaling 29 or higher, and nine of our participants' BDI scores fell within this range.

3.2. *Results*

A univariate ANOVA was conducted on the scores for the five CANTAB subtests, delayed match to sample (DMS), paired associate learning (PAL), pattern recognition memory (PRM), spatial recognition memory (SRM) and rapid visual information processing (RVP), to test for significant differences among the healthy ($n=146$) vs. potentially depressed (i.e. BDI score of 29 or higher, $n=9$) individuals. For the DMS, a baseline-corrected score was calculated by subtracting the percent correct performance for the longest delay (12 s) from the percent correct score for the zero delay, under the hypothesis that the performance at the longest delay would be impaired in depressed individuals, presumably reflecting a neurogenesis deficit. The only test on which the groups differed significantly was the Delayed Match to Sample ($F(1,153)=4.03$, $p<.05$), as shown in Fig. 4a). On all other tests, the groups were indistinguishable, as can be seen in Figs. 4b–e. As found in many previous studies, individuals' depression (BDI) scores were highly correlated with their stress (PSS) scores (Pearson correlation coefficient=.796, $p<.001$) and also with their anxiety (BAI) scores (Pearson correlation coefficient=.699, $p<.001$).

3.3. *Discussion*

Both the CANTAB paired associates learning task and the delayed match to sample task appear to be sensitive to hippocampal/medial-temporal lobe damage (Owen et al., 1995), consistent with lesion studies in rodents (e.g. Morris et al., 1999; Gilbert and Kesner, 2002; Day et al., 2003), and a mounting body of evidence from hippocampal volumetric and functional imaging studies in humans using paired associates and DMS/DNMS (e.g. Starkman et al., 1992; Elliott and Dolan, 1999; de Zubicaray et al., 2001; Monk et al., 2002; Meltzer and Constable, 2005; Law et al., 2005). Thus, our finding of a selective deficit on the DMS task at the longest delay, in spite of intact performance on other hippocampal-dependent memory tasks, is consistent with our hypothesis of a selective deficit on neurogenesis-dependent forms of learning and memory. In the Introduction, we suggested that new neurons may be critical on tasks that require bridging information across time delays. The CANTAB DMS task requires that novel complex objects must be maintained in visual working memory across variable delays for subsequent matching. Human imaging studies have shown hippocampal activation in DMS tasks employing CANTAB-like stimuli (Monk et al., 2002), and more generally, in tasks involving visual working memory for novel objects (Ranganath et al. 2005; Schon et al., 2004).

4. General discussion and conclusions

The long-term goal of this research is to understand hippocampal memory mechanisms, and in particular, the functional

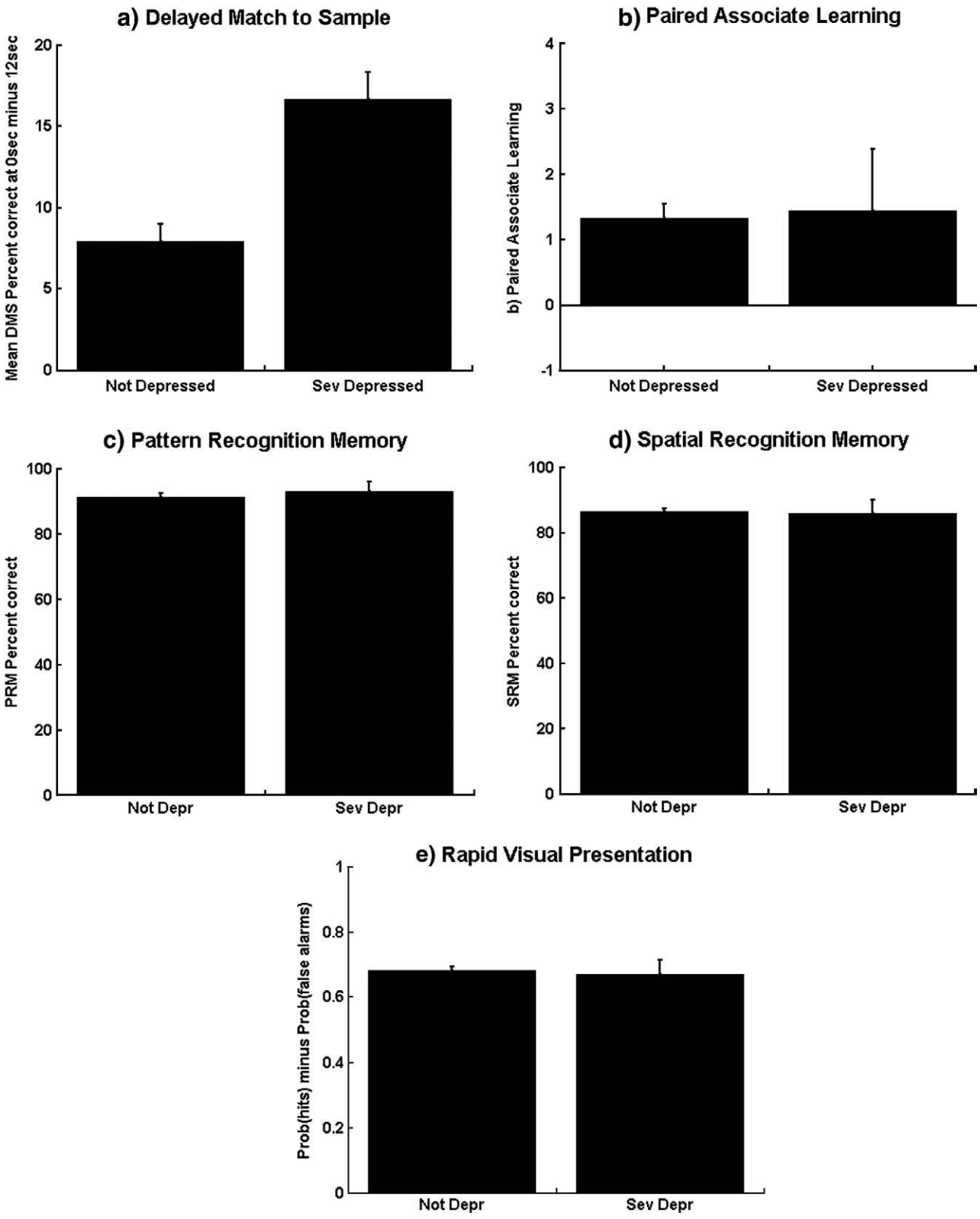

Fig. 4 – Mean performance (with standard error bars) on the five CANTAB tests, for healthy (left bars) and self-identified depressed (right bars) individuals. (a) Delayed match to sample (DMS), percent correct at 0 s minus percent correct at 12 s. (b) Paired associate learning (PAL) total errors. (c) Pattern recognition memory (PRM) percent correct. (d) Spatial recognition memory (SRM), percent correct. (e) Rapid visual presentation (RVP), probability of hits minus probability of false alarms.

significance of adult hippocampal neurogenesis in memory. Evidence from animal studies suggests that neurogenesis in the hippocampus may be important for forming highly distinctive memories for episodes—events that unfold over time. A deficit in neurogenesis should interfere with long-term memory retention on a scale of weeks to months, as is consistent with our hypothesis that the model simulations reported here. We also hypothesize that, in young adults who self-identify as having depressive symptoms, a reduction in neurogenesis may be one of the earliest detectable changes in the brain, leading to a specific pattern of memory deficits. Animals with reduced neurogenesis exhibit deficits on tasks requiring linkage of events across time, e.g. DNMS at long delays and contextual fear conditioning (Winocur et al., 2006) and trace conditioning (Shors et al., 2001), while our computational model predicts deficits on tasks in which there is the potential for high interference (Becker, 2005). The selective deficit in long-delay DMS exhibited by our group who self-identified as having depressive symptoms, despite normal performance on other cognitive tasks, is consistent with this hypothesis. In ongoing research, we are testing the same population on an A-B A-C paired associates verbal learning task. We predict that people in a first episode of MDD will have difficulty forming distinct memory representations of overlapping word pairs from the A-B and A-C lists (e.g. "sugar-toothache" and "sugar-syrup") and will therefore show greater proactive interference (encoding and recalling A-C pairs, having previously learned the A-B pairs) and/or retroactive interference (first learning the A-B pairs, then the A-C pairs, and then recalling the original A-B pairs).

A key assumption in the results reported here is that people who self-identify as having depressive symptoms have reduced neurogenesis. This assumption is based on evidence primarily from animal models of depression employing chronic stress, in which reductions of neurogenesis are observed (e.g. Gould et al., 1998; and for a review, see Becker and Wojtowicz, 2007). Moreover, there is a large body of evidence indicating that stress is a causal factor in the pathogenesis of human major depressive disorder (see e.g. Kendler et al., 2004). Thus it is reasonable to assume that in humans, as in non-human animals, stress and depression are associated with reduced neurogenesis. Our results, namely, a selective deficit on the DMS task at long delays, are also consistent with animal studies showing that suppression of neurogenesis causes a deficit in delayed non-match to sample at long delays (Winocur et al., 2006). A more direct test of our assumption of reduced neurogenesis in people who are stressed/depressed might be possible in future using recent innovations in structural MRI and MR spectroscopy for detecting physiological correlates of neurogenesis non-invasively in the human brain (Manganas et al., 2007; Pereira et al., 2007).

While a reduction in hippocampal neurogenesis impairs performance on certain memory tasks, there may be other tasks for which having fewer new neurons leads to superior memory performance. A recent study by Saxe et al. (2007) found a paradoxical improvement in working memory in animals with reduced neurogenesis, on a variant of the 8-arm radial maze task in which there is the potential for interference from past learning trials. In this version of the task, it is advantageous to remember only the sequence of rewarded arms for the current trial and ignore those sequences of arms rewarded on previous occasions. In this case, animals with reduced neurogenesis outperformed controls. This finding is consistent with the predictions of our computational model that neurogenesis contributes to distinct memory representations for highly similar events. Normally, this form of encoding would be advantageous in reducing interference. However, on tasks in which it is advantageous to forget what occurred in similar situations and simply respond according to the current context, a reduction in hippocampal neurogenesis would actually be beneficial.

In addition to stress, many other environmental and lifestyle factors affect neurogenesis. For example, exercise enhances neurogenesis both in rodents and humans (van Praag et al., 1999; Pereira et al., 2007), while alcohol bingeing reduces neurogenesis (Crews et al., 2006; Nixon and Crews, 2002). We are currently investigating the correlation between exercise, alcohol-bingeing and performance on neurogenesis-dependent learning and memory tasks in undergraduates with low and high levels of depressive symptoms.

The effect of exercise on neurogenesis is particularly significant given its clinical relevance in treating depression. This antidepressant effect of exercise could be mediated, at least in part, via its effects on neurogenesis. Selective serotonin reuptake inhibiting (SSRI) antidepressants enhance neurogenesis (Malberg et al., 2000, and there is some evidence from animal models that their behavioral efficacy in treating depressive symptomatology may be causally related to their ability to restore neurogenesis (Santarelli et al. 2003); moreover, the behavioral efficacy of running as an anti-depressant is correlated with enhanced neurogenesis (Bjørnebekk et al., 2005). This lends support to the notion that SSRIs and other antidepressant treatments such as exercise and electroconvulsive therapy may exert their clinical action, at least in part, by restoring normal hippocampal function including neurogenesis, a hypothesis that we elaborate on in a recent article (Becker and Wojtowicz, 2007).

If a reduction in neurogenesis is, as predicted, a marker for the earliest stages of conversion from stressed to depressed, the non-invasive monitoring of people with stress-related adjustment disorders may allow for the identification of those at highest risk for conversion to full-syndrome depressive episodes.

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