Why has adult hippocampal neurogenesis had so little impact on psychiatry?

Author information:
Kathy Y. Liu, Robert Howard

Kathy Y. Liu, BA, MB BChir, MRCPsych, Division of Psychiatry, University College London, UK; **Robert Howard,** BA, MB BS, MRCPsych, MD, Division of Psychiatry, University College London, UK.
Correspondence: Kathy Liu, Division of Psychiatry UCL, Maple House 149 Tottenham Court Road, London W1T 7NF. Email: kathy.liu@ucl.ac.uk

Kathy Liu is an Academic Clinical Fellow in Old Age Psychiatry at University College London and Camden and Islington NHS Foundation Trust. Robert Howard is Professor of Old Age Psychiatry at University College London and Honorary Consultant Old Age Psychiatrist at Camden and Islington NHS Foundation Trust.

Declaration of interest
None.

Abstract
Hippocampal neurogenesis continues throughout adult life and potentially plays a crucial role in mood and cognitive disorders. We summarise the preclinical insights and potential translational steps that could be taken to investigate the role and importance of this phenomenon in disease and health in humans.

Adult hippocampal neurogenesis
In 1913, Santiago Ramón y Cajal concluded that neurons are exclusively generated prenatally, and the notion that no further neurons are produced after birth has remained a central dogma within neuroscience.

Within the last decade, this view has been challenged following the demonstration that new brain cells are generated within specific neurogenic sites throughout adulthood. These are the dentate gyrus of the hippocampus and the subventricular zone[1]. In humans, adult neurogenesis undoubtedly occurs in the hippocampus [2], but its function and importance has yet to be convincingly demonstrated because of a paucity of clinical

studies and lack of a validated measure of new neuron function. Nevertheless, valid methods to index neurogenesis are achievable [3], and given the potential of an understanding of neurogenesis to advance treatments for mental health disorders, psychiatrists should explore this area.

What is adult hippocampal neurogenesis for?

A model for the function of adult-born neurons in the dentate gyrus is emerging as evidence from animal work accumulates [4]. With greater excitability and plasticity, new neurons in the dentate gyrus can modulate the activity of mature neurons, enhancing the ability to learn and discriminate between highly similar contexts in a neural process known as pattern separation. This involves successful recall of two distinct memories with overlapping features, for example, where you parked your car today versus the place you parked it yesterday. By preventing interference between novel and older memories, neurogenesis may also enhance the ability to adapt to new contexts where old rules are replaced with new associations, as in reversal learning.

Why might neurogenesis be important for psychiatry?

Impaired neurogenesis would reduce the ability to learn that a new context is safe once a stressful situation has finished. A consequent persisting negative emotion, such as fear or anxiety, could then plausibly contribute to psychopathology, for example in depression, anxiety or post-traumatic stress-disorder. Hence, factors that impair neurogenesis in rodents and nonhuman primates, such as chronic stress with hypothalamic-pituitary-adrenal axis (HPA) hyperactivity and elevated glucocorticoid levels, lead to animal models of depressive behaviours [5]. A recent study has demonstrated the neurogenesis-inhibition that accompanies cancer chemotherapy and the emergence of depressive behaviours in mice [6], explaining the depressive and cognitive symptoms described in chemotherapy patients. Evidence that this may also apply to humans includes the neurogenesis-inhibiting effect of glucocorticoids on hippocampal stem cells *in vitro* [7], and the observation that depressed patients perform poorly on pattern separation tasks [4], have lower levels of circulating neurogenic factors (BDNF) that correlate with symptom severity [8] and reduced newborn hippocampal

neurons at post-mortem [9].

If impaired neurogenesis can lead to depressive and anxiety symptoms, could its recovery underlie antidepressant treatment effects? There is good evidence to suggest that this could be the case. Administration of antidepressants are associated with increased neurogenesis in rodents, nonhuman primates, human hippocampal stem cells *in vitro* and human post-mortem brain tissue, with some rodent studies finding that neurogenesis is necessary for some of the behavioural effects of SSRIs[4]. Intriguingly, the time course of maturation of newly generated neurons in the dentate gyrus generally coincides with the time to therapeutic action of antidepressants. Non-pharmacological treatments for depression such as electroconvulsive shock therapy and physical exercise have also been shown to restore neurogenesis in animals, and human performance on a pattern separation task improves after an exercise intervention[10].

The observation that adult hippocampal neurogenesis declines with increasing age could explain some of the reduced cognitive flexibility and impaired memory performance associated with normal ageing, mild cognitive impairment (MCI) and neurodegenerative conditions such as Alzheimer disease (AD). Many of the molecular players in AD are also modulators of neurogenesis[11] and performance on tasks designed to test pattern separation ability show an age-MCI-AD continuum[12].

Although there is increasing evidence for the role of neurogenesis in mood and cognitive disorders, there are some caveats to consider. Any effects of impaired neurogenesis are likely to be context-dependent. For example, chronic stress may be necessary if depressive behaviours are to arise through this mechanism. Further, neurogenesis is likely to be one of several potential mechanisms of antidepressant action and may not necessarily underlie all of the behavioural effects of treatment. Finally, findings from animals can never be wholly applied to humans, although the accumulated evidence provides testable hypotheses that can be translated to human studies.

How can neurogenesis be investigated in humans?

There is currently no method to directly detect and measure hippocampal neurogenesis in humans. One strategy to clarify the precise relationship between neurogenesis and cognition/mood could involve combination of different correlates of neurogenesis to optimise convergent validity. For example, observing within a population whose impaired neurogenesis would be expected to recover that these correlates improve in accordance with the known maturation time of human hippocampal stem cells (4-8 weeks)[13] would have predictive validity. Demonstration of a temporal dissociation between the recovery of putative neurogenesis-dependent correlates and other non-neurogenesis dependent measures would also be informative. These approaches could be nested within clinical trials, for example, in cancer patients after receiving a discrete regimen of chemotherapy or depressed patients about to start antidepressant therapy. It can be expected that any improvement in mood will be temporally associated with improvements in neurogenesis correlates (described below).

A combination of neuropsychology, neuroimaging and biological correlates can indirectly measure neurogenesis. Pattern separation tasks are convenient and easy to administer tests designed to probe the function of new neurons in different cognitive domains, for example emotional, spatial or temporal pattern separation. These can be combined and used in conjunction with non-neurogenesis dependent cognitive tasks (e.g. episodic and working memory, attention, executive function) to reveal a performance dissociation compared to a control group and between two time points measured before and after presumed neural stem cell maturation.

The validity of pattern separation tasks as markers for neurogenesis can be tested by functioning magnetic resonance imaging (fMRI) to show that performance is associated with activity in the dentate gyrus[14]. The small size of individual hippocampal subfields makes them notoriously difficult to delineate and measure, however the increasing availability of 7-Tesla MRI scanners could provide insight into dentate gyrus volume changes which may be associated with neurogenesis.

Therapeutic implications

If human studies uncover a role for hippocampal neurogenesis in neuropsychiatric disorders, existing treatments and novel neurogenic agents could be prescribed to target this process in patients with depression, neurodegenerative conditions and those being treated with chemotherapy. Studies investigating neurogenesis can identify potentially targetable molecular mechanisms for future antidepressants [7]. Increasingly, research is also revealing a possible role for neurogenesis in schizophrenia and drug addiction[15]. Stem-cell based therapies are also on the horizon; impending clinical trials for Parkinson's disease[16] may pave a way for future human hippocampal stem cell transplants.

Conclusion

Adult hippocampal neurogenesis represents a new and promising area of enquiry for psychiatry, requiring researchers to bridge the translational divide between existing animal work and human studies. Better demonstration of the role of this process and its therapeutic potential in common neuropsychiatric conditions would lead to a paradigm shift in how we assess and manage disorders of cognition and mood in our patients.

References

1 Gage FH. Mammalian neural stem cells. *Science* 2000; **287**: 1433–8.

2 Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, *et al.* Dynamics of hippocampal neurogenesis in adult humans. *Cell* 2013; **153**: 1219–27.

3 Ho NF, Hooker JM, Sahay A, Holt DJ, Roffman JL. In vivo imaging of adult human hippocampal neurogenesis: progress, pitfalls and promise. *Mol Psychiatry* 2013; **18**: 404–16.

4 Anacker C, Hen R. Adult hippocampal neurogenesis and cognitive flexibility - linking memory and mood. *Nat Rev Neurosci* 2017. doi:10.1038/nrn.2017.45.

5 Murray F, Smith DW, Hutson PH. Chronic low dose corticosterone exposure decreased hippocampal cell proliferation, volume and induced anxiety and depression like behaviours in mice. *Eur J Pharmacol* 2008; **583**: 115–27.

6 Egeland M, Guinaudie C, Du Preez A, Musaelyan K, Zunszain PA, Fernandes C, *et al.* Depletion of adult neurogenesis using the chemotherapy drug temozolomide in mice induces behavioural and biological changes relevant to depression. *Transl Psychiatry* 2017; **7**: e1101.

7 Anacker C, Cattaneo A, Luoni A, Musaelyan K, Zunszain PA, Milanesi E, *et al.* Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. *Neuropsychopharmacology* 2013; **38**: 872–83.

8 Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol* 2008; **11**: 1169–80.

9 Lucassen PJ, Stumpel MW, Wang Q, Aronica E. Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. *Neuropharmacology* 2010; **58**: 940–9.

10 Déry N, Pilgrim M, Gibala M, Gillen J, Wojtowicz JM, Macqueen G, *et al.* Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. *Front Neurosci* 2013; **7**: 66.

11 Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. *Mol Neurodegener* 2011; **6**: 85.

12 Ally BA, Hussey EP, Ko PC, Molitor RJ. Pattern separation and pattern completion in Alzheimer's disease: evidence of rapid forgetting in amnestic mild cognitive impairment. *Hippocampus* 2013; **23**: 1246–58.

13 Yu DX, Di Giorgio FP, Yao J, Marchetto MC, Brennand K, Wright R, *et al.* Modeling hippocampal neurogenesis using human pluripotent stem cells. *Stem Cell Reports* 2014; **2**: 295–310.

14 Liu KY, Gould RL, Coulson MC, Ward EV, Howard RJ. Tests of pattern separation and pattern completion in humans-A systematic review. *Hippocampus* 2016; **26**: 705–17.

15 DeCarolis NA, Eisch AJ. Hippocampal neurogenesis as a target for the treatment of mental illness: a critical evaluation. *Neuropharmacology* 2010; **58**: 884–93.

16 Barker RA, Parmar M, Kirkeby A, Björklund A, Thompson L, Brundin P. Are Stem Cell-Based Therapies for Parkinson's Disease Ready for the Clinic in 2016? *J Parkinsons Dis* 2016; **6**: 57–63.