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Adult hippocampal neurogenesis and cognitive flexibility — linking memory and mood

Christoph Anacker[1] and **René Hen**[1,2,3]

[1]Department of Psychiatry, Columbia University and Research Foundation for Mental Hygiene, New York State Psychiatric Institute, 1051 Riverside Drive, New York 10032, New York, USA

[2]Department of Neuroscience, Columbia University, Kolb Annex, 40 Haven Ave, New York 10032, New York, USA

[3]Department of Pharmacology, Columbia University, 630 West 168th Street, New York 10032, New York, USA

Abstract

Adult hippocampal neurogenesis has been implicated in cognitive processes, such as pattern separation, and in the behavioural effects of stress and antidepressants. Young adult-born neurons have been shown to inhibit the overall activity of the dentate gyrus by recruiting local interneurons, which may result in sparse contextual representations and improved pattern separation. We propose that neurogenesis-mediated inhibition also reduces memory interference and enables reversal learning both in neutral situations and in emotionally charged ones. Such improved cognitive flexibility may in turn help to decrease anxiety-like and depressive-like behaviour.

Mood and anxiety disorders are heterogeneous in terms of their aetiology and pathophysiology, which complicates the challenge of identifying specific neural and molecular correlates that may be targeted by future treatments. To gain an integrative understanding of the neurobiology that underlies psychiatric disorders, clinical neuroscience has begun to focus on understanding the complex neural circuitry that is involved in these conditions. Such an approach is a crucial step towards developing novel circuit-based therapeutic strategies.

The hippocampus has considerable importance for cognition and mood. One of the most fascinating features of this brain region is its unusual capacity for adult neurogenesis, a process by which new neurons are continuously generated in the dentate gyrus, where they develop into mature neurons and functionally integrate into the existing neural circuitry[1]. In humans, 700 new adult-born neurons are added to this circuitry each day in a middle-aged adult[2]. How such a relatively small number of young neurons functionally contributes to complex behaviours and psychiatric disorders remains unclear.

Competing interests statement

The authors declare no competing interests.

In this Review, we primarily discuss data from rodent studies that have investigated how adult-born neurons contribute to information encoding in the dentate gyrus both by integrating information as independent encoding units and by inhibiting the activity of mature granule cells. We discuss how this regulation of dentate gyrus function by adult neurogenesis affects the cognitive processes of reversal learning and cognitive flexibility, which may have important implications for both memory and mood. We conclude by proposing that targeting dentate gyrus activity and neurogenesis-dependent cognitive processes, such as pattern separation and cognitive flexibility, may be promising new leads in the treatment of patients with mood disorders.

The hippocampal dorsal–ventral axis

Animal and human studies have shown that the hippocampus is a heterogeneous structure with gradually segregated functional differences along its dorsoventral axis[3–6]. In rodents, lesion studies and optogenetics have been used to examine the differential functions of the dorsal and the ventral hippocampal poles. These studies have shown that lesions of the dorsal hippocampus primarily impair cognition and spatial learning and that optogenetic inhibition of dorsal dentate gyrus granule cells impairs contextual memory encoding[7]. In humans, the posterior hippocampus, which is analogous to the dorsal hippocampus in rodents, is larger in individuals who require a large capacity for processing spatial and contextual information, such as taxi drivers[8]. High activity in the posterior hippocampus has also been found in non-human primates after spatial learning[9].

By contrast, lesions of the ventral hippocampus alter emotional behaviour, social interactions[10] and stress resilience[11–14], and optogenetic activation of ventral dentate gyrus granule cells decreases innate anxiety-like behaviour in rodents[7]. The human anterior hippocampus, which is analogous to the ventral hippocampus in rodents, is smaller in unmedicated patients with depression and larger in antidepressant-treated patients than in healthy individuals[15]. Non-human primates with increased anxiety-like behaviour and neuroendocrine activity also show an increase in metabolism in the anterior hippocampus[16,17].

Dorsoventral differences are also observed for neurogenesis. Specifically, in rodents, the number of adult-born cells that express doublecortin, a marker of immature neurons, is higher in the dorsal than in the ventral dentate gyrus[18–21]. However, the number of mature adult-born neurons is higher in the ventral than in the dorsal dentate gyrus[20,22], suggesting that, overall, more neurons may be added to the ventral dentate gyrus. In accordance with the functional segregation between the dorsal and the ventral hippocampus, dorsal neurogenesis is increased in rodents that undergo complex spatial and contextual stimulation in an enriched environment[20,22,23]. By contrast, chronic stress models, such as social defeat, social submissiveness and unpredictable chronic stress, are associated with a decrease in neurogenesis in the ventral dentate gyrus[20,22,24,25]. In addition, chronic treatment with antidepressants increases neurogenesis predominantly in the ventral dentate gyrus and counteracts the effects of stress in both rodents[25] and humans[26].

In the hippocampus, the basic cellular connectivity of the trisynaptic circuit is maintained throughout its dorsoventral extent[4,27]. However, the afferent and efferent connectivity of the hippocampus markedly differs between the dorsal and the ventral poles[6]. In line with its role in stress processing and mood, the ventral hippocampus is at the centre of a complex neural circuit that regulates anxiety and emotion (FIG. 1. Recent studies have shown that this neural circuit includes glutamatergic projections from the ventral hippocampus to several downstream processing structures that are involved in anxiety regulation, stress responses and reward seeking. For example, projections to the medial prefrontal cortex (mPFC) promote anxiety, context aversion and behavioural inhibition[28,29], and bidirectional connections between the ventral hippocampus and the amygdala are implicated in fear processing and social interaction. These amygdala projections have also been proposed to consolidate memories with emotional content[30]. Moreover, projections from the ventral hippocampus to the nucleus accumbens regulate dopamine release from the ventral tegmental area and are implicated in pleasure and reward seeking[31], as well as in regulating stress susceptibility and resilience[32]. The ventral hippocampus is also an important regulator of the neuroendocrine system, which inhibits hypothalamus–pituitary–adrenal (HPA) axis activity and glucocorticoid release. At the level of the neural circuitry, ventral hippocampal projections activate GABAergic interneurons in the bed nucleus of the stria terminalis, which in turn inhibit the production of corticotropinreleasing hormone from the paraventricular nucleus of the hypothalamus[33–35]. These ventral hippocampal projections may be important in the regulation of mood and anxiety (discussed in detail below).

Dentate gyrus function

The ability of the dentate gyrus to generate new neurons has stimulated research on how these adult-born neurons influence hippocampal information processing. In a 12-week-old adult mouse, the number of 4–6-week-old adult-born neurons is approximately 10% of the total number of developmentaly born, mature granule cells[36–38]. These young adult-born neurons in their critical period of development have distinct electrophysiological properties, including high input resistance and a lack of GABAergic inhibition, which results in these cells having a greater propensity for hyperexcitability and exhibiting lower activation thresholds than mature granule cells. Young adult-born neurons also show enhanced plasticity and long-term potentiation, which are mediated by NR2B-containing NMDA receptors[36,39,40]. In addition, 4–6-week-old neurons make a unique contribution to hippocampus-dependent behaviours[41]. Below, we discuss how adult-born neurons may regulate complex aspects of information processing in the dentate gyrus microcircuit by encoding discrete spatial and temporal information as independent encoding units and by regulating the activity of mature granule cells.

Adult-born neurons are recruited by learning.

Rodent studies have suggested that hippocampus-dependent learning tasks that involve temporal-based associations or spatial contextual navigation promote and, indeed, require adult neurogenesis. By contrast, various studies have indicated that non-hippocampus-dependent learning does not require adult neurogenesis[42–46] (but see also REFS 47–51). In line with a role for young adult-born neurons in novelty encoding and learning, navigating in

novel and enriched environments also increases adult neurogenesis[23,52,53]. Studies using immediate early genes as markers of neuronal activity showed that 2–4-week-old adult-born cells are recruited during spatial learning, fear memory retrieval, or stressful and anxiogenic conditions[54–57,58]. In addition to contextual information encoding, computational models and electrophysiological studies suggest that young neurons may encode temporal information during their critical period[59,60]. As the population of young neurons matures, these cells leave their critical period, and events that are far apart in time would therefore be encoded by different, non-overlapping hyperexcitable cell populations. By contrast, closely related events would be encoded by a similar population of young neurons, which could be a potential mechanism for associating proximally dated memories[59]. In support of this idea, adult-born neurons that are activated by exposure to an enriched environment during the first 3 weeks of development are more likely to be reactivated by re-exposure to the same environment once they have reached maturity[61]. However, such a temporal coding model relies on the assumption that, owing to their hyperexcitability, young adult-born neurons are indeed preferentially activated by learning compared with mature granule cells[58], a finding that is not yet well established[62]. Nevertheless, the addition of new neurons to the dentate gyrus may be an efficient method of encoding new information without disrupting previously stored memories[63–65].

Adult-born neurons modulate dentate gyrus function.

In addition to their proposed role in encoding new information, adult-born neurons also modulate the activity of mature granule cells. For example, the ablation of neurogenesis by X-ray irradiation increases dentate gyrus gamma burst amplitude and increases the number of active mature granule cells during reversal learning tasks[66,67]. Conversely, increasing neurogenesis reduces dentate gyrus excitability[68], and optogenetic stimulation of adult-born neurons reduces mature granule cell activity[69].

In vivo, this inhibitory effect of young neurons is specific to anxiogenic conditions and neurogenesis-dependent tasks. For example, neurogenesis ablation only increases immediate early gene expression in the dentate gyrus during neurogenesis-dependent conflict situations[67]. Accordingly, optogenetic activation of adult-born neurons decreases dentate gyrus activity in conditions of novelty and anxiety, whereas the activation of a similar number of mature granule cells has no effect on the activity of the remaining mature cells[69]. However, *in vitro* slice electrophysiology has shown that, under baseline conditions, mature (8-week-old) adult-born neurons are stronger inhibitors of the dentate gyrus than young (4-week-old) neurons[70]. These discordant data emphasize the need to determine the exact age at which and the exact behavioural situations in which adult-born neurons exert unique inhibitory control over mature granule cells to modify the dentate gyrus network (BOX 1).

Considering that stress and glucocorticoids increase dentate gyrus synaptic currents *in vitro*[71] and that stress increases dentate gyrus activity *in vivo*[56], neurogenic inhibition of the dentate gyrus may be particularly relevant for stress-induced psychopathology, including anxiety and depression. Changing dentate gyrus activity may also ultimately determine the strength of hippocampal projections to downstream associated brain structures (FIG. 1).

Therefore, neurogenesis may exert potent effects on behaviour by modulating the neuronal networks of mood and anxiety through activity changes in the hippocampus.

Neurogenesis, learning and memory

Much research has examined the effects of mood on memory encoding and retrieval[72]. However, less is known about how memory can influence mood and anxiety. We propose below that some of the effects of neurogenesis on mood and anxiety may not be independent of the effects of neurogenesis on cognition.

Neurogenesis and pattern separation.

A major task of a functional memory system is to encode highly similar pieces of information discretely and without interfering with previously established memories. The dentate gyrus has been proposed to accomplish this task by disambiguating similar contextual representations through the computational process of pattern separation[73,74]. In the dentate gyrus, neuronal inputs from the entorhinal cortex are first encoded by sparse populations of granule neurons that form distinct representations of mnemonic information with high similarity[75–77]. The addition of new neurons with enhanced plasticity to the dentate gyrus has indeed been proposed to be most efficient in encoding new information while avoiding the loss of memory retrieval properties[64,65,78]. This sparsely encoded information in the dentate gyrus is subsequently relayed to CA3 pyramidal neurons, which store these representations in auto-associative cellular networks that allow memory retrieval when partial cues of incomplete aspects of that memory are being detected (pattern completion)[75,79,80].

Experimentally, ablating neurogenesis or the optogenetic silencing of adult-born neurons impairs the ability to discriminate highly similar contexts (high interference)[7,51,77,81–83]. Accordingly, increasing the number of adult-born neurons[84–87] or their functional integration into the dentate gyrus microcircuit[88] enhances the ability to discriminate highly similar contexts. By contrast, discriminating contexts that are very different (low interference) is not dependent on neurogenesis[37,51,77,84,85,89].

According to computational models, sparse activity of the dentate gyrus is indeed necessary for pattern separation[73,90–92]. Young neurons themselves may thus be rather ineffective at separating similar events, as their hyperexcitability may make them broadly tuned to new, temporally related information[37,59]. By contrast, mature granule cells are proposed to be more efficient in the sparse encoding of contextual information owing to their higher excitation threshold[37,63]. It has thus been suggested that adult-born neurons may function as ‘pattern integrators’ that are able to associate similar events with each other, as opposed to carrying out pattern separation[63]. Such a pattern integration function, which may provide a means by which to encode temporal associations, may not conflict with a second role for young neurons in pattern separation. On the basis of the activation of local inhibitory circuits (BOX 1), highly excitable young cells may simultaneously inhibit the population of mature cells to achieve the sparse activation that is required for pattern separation. In this hypothetical dual model, young adult-born neurons would act as pattern integrators to

encode temporal associations of information and as indirect ‘pattern separators’ that inhibit mature granule cells to facilitate sparse coding.

The dentate gyrus and emotional memory engratns.

To elucidate how fear and anxiety are encoded by the hippocampus, rodent studies have used contextual fear discrimination learning and indelible labelling of active cells using immediate early gene-dependent tagging strategies. When mice learn to associate a context with an aversive event, such as a footshock, that fear-memory is encoded by a cellular representation in the hippocampus. When mice are re-exposed to the same context in which they had previously received the footshock, a proportion of the cells that were active during encoding are also recruited during the retrieval of that memory. By contrast, exposure to a novel context, in which fear was never experienced, activates a different population of neurons in the dentate gyrus[93–95].

These memory traces, or engrams, in the dentate gyrus are indeed necessary and sufficient to produce fear and anxiety-like behaviours. For example, optogenetic activation of cells that are labelled during the encoding of a fearful context can elicit a fear response in a neutral context in which fear was never experienced[96]. Conversely, the silencing of engrams of a fearful experience suppresses fear and anxiety-like behaviour during memory recall[94]. A fear memory can also be converted into a rewarding memory when the fear-encoding engram is activated during the experience of a reward. As a result, mice that associate the original fear engram with reward exhibit less freezing in the aversive context. Similarly, the memory of a reward can be replaced by an aversive memory when the reward engram is activated during exposure to a fearful context[97]. Activating these dentate memory engrams of positive experiences engages excitatory projections from the basolateral amygdala to the nucleus accumbens and ameliorates stress-induced anxiety-like and depressive-like symptoms[98].

Neurogenesis and emotional memory engrams.

In agreement with the crucial role of neurogenesis in pattern separation, adult-born neurons are necessary for encoding information in non-overlapping memory engrams. Indeed, ablation of neurogenesis, either by hippocampal X-ray irradiation or by optogenetically silencing adult-born granule cells, impairs engram reactivation and weakens the memory of a fearful event[37,41,94]. However, ablation of neurogenesis impairs reactivation in CA3 but not in the dentate gyrus itself[94], suggesting that neurogenesis regulates information processing across hippocampal subregions[99].

In addition to pattern integration and pattern separation during memory encoding, neurogenesis has also been proposed to promote the clearance of previously established memories[100,101]. This post-encoding memory erasure may act concurrently with pattern separation to reduce proactive interference, a process by which previously learned information impedes the learning of new information that has a highly similar content. This memory erasure may depend on the ability to inhibit mature granule cells that store a previously encoded memory (FIG. 2) but may not necessarily compromise previously

learned information that has already been transferred from the temporary memory storage of the hippocampus to the permanent cortical storage areas.

Neurogenesis and cognitive flexibility.

Although cognitive flexibility is mostly attributed to the PFC, human functional MRI (fMRI) and positron emission tomography studies[102,103], as well as rodent reversal learning experiments[67,104–107], have suggested that it may also require the hippocampus. Computational studies have also proposed that hippocampal neurogenesis may be necessary for cognitive flexibility, as it allows the avoidance of interference between novel and previously formed memories[64,65,78,108–110]. This was first experimentally demonstrated by studies showing that mice with reduced neurogenesis were impaired in finding a safety platform in the Morris water maze[105,106]. Accordingly, environmental enrichment, which increases neurogenesis[23], also increased the ability of an animal to apply more efficient spatial search strategies in this task after a platform location was changed[111]. These findings were extended by studies using similar versions of the Morris water maze task[112,113], touch-screen discrimination tasks[107] or active place-avoidance tasks in which neurogenesis is required for learning that the position of a shock zone on a rotating platform has changed[67]. In all these experiments, neurogenesis was only required for learning the reversal of a rule and not for learning the initial rule (for example, neurogenesis was not required for initially finding the safety location). This suggests an emerging new function for neurogenesis in reversal learning and cognitive flexibility, in addition to its role in pattern separation during the encoding of new memories. In accordance with the memory clearance hypothesis[78,100], neurogenesis may promote the erasure of previously learned associations; for example, where a safety platform is hidden in the Morris water maze task. ‘Forgetting’ the old association may consequently facilitate the learning of novel associations, such as the new location of the safety platform[101] (FIG. 2). It is conceivable that such a process requires the inhibition of mature dentate gyrus granule cells to silence previously established engrams and to enable the formation of new memory traces and, ultimately, cognitive flexibility. We therefore propose a model by which neurogenesis-dependent inhibition of the dentate gyrus facilitates cognitive flexibility by allowing new, distinct memories to be formed faster (FIG. 2). Below, we discuss how this effect of neurogenesis on cognitive flexibility may contribute to mood and anxiety disorders.

Neurogenesis, mood and anxiety

The effects of stress on neurogenesis, depression and anxiety.

Adult neurogenesis has been extensively described as a key function of the hippocampus that is sensitive to the effects of stress[33,35,114]. Chronic stress procedures for 2–8 weeks, such as chronic social defeat[24], unpredictable chronic mild stress[20,115–117], chronic immobilization[118], prenatal stress[119,120] and early life stress[121], reduce neurogenesis in rodents. Similar effects are also observed in non-human primates, in which social isolation or subordination reduces neurogenesis and causes anhedonia[122–124] These stress effects on neurogenesis occur most prominently in the ventral portion of the hippocampus[22,24] and seem to be relevant to the clinical situation, as patients with depression also exhibit decreased levels of neurogenesis[125]. Most rodent studies have demonstrated that reducing or

enhancing neurogenesis modulates anxietylike and depressive-like behaviours only in response to stress and that neurogenesis does not modulate these behaviours if stress is absent[115,117,126–128]. However, some studies have suggested that even without prior stress, neurogenesis ablation increases innate anxiety-like and approach-avoidance behaviour[126,129].

The crucial role of neurogenesis in learning and memory suggests that changes in neurogenesis, for example, as a result of chronic stress, may ultimately affect intra-hippocampal information processing and information relay to downstream connected brain structures, such as the amygdala and the hypothalamus, which are crucial for regulating anxiety and neuroendocrine function (FIG. 1). Indeed, changes in neurogenesis may affect basolateral amygdala activity after stress, although a causal relationship remains to be established[118].

Neurogenesis and the neuroendocrine system.

Hyperactivity of the HPA axis and elevated glucocorticoid levels are potent mediators of stress effects on neurogenesis. For example, chronic stress does not impair neurogenesis in adrenalectomized rodents in which glucocorticoids are maintained at consistently low levels[24]. Conversely, chronic treatment with exogenous glucocorticoids precipitates anxiety-like and depressive-like behaviour and reduces neurogenesis in rodents through a glucocorticoid receptor-mediated effect[127,128,130–132]. Glucocorticoids have also been shown to reduce neurogenesis in *in vitro* human hippocampal stem cell culture models[133,134]. In addition to being particularly vulnerable to the effects of glucocorticoids, neurogenesis has been implicated in regulating the body's response to, and recovery from, stress. Glutamatergic projections from the ventral hippocampus activate GABAergic inhibitory interneurons in the bed nucleus of the stria terminalis, which in turn inhibit hypothalamic paraventricular nucleus neurons and glucocorticoid release from the adrenal cortex[33–35]. Without neurogenesis, mice exhibit impaired HPA axis feedback inhibition and an increased glucocorticoid surge after acute stress compared with mice in which neurogenesis is intact[135,136]. These findings suggest that neurogenesis is required to maintain appropriate hippocampal inhibitory control over the HPA axis, and that impairments in neurogenesis (for example, after chronic stress) may exacerbate glucocorticoid abnormalities and reduce neurogenesis. The resulting persistent HPA axis hyperactivity may set in motion a vicious cycle, in which glucocorticoid abnormalities continue to reduce neurogenesis, ultimately leading to long-term disturbances in stress reactivity and sustained anxiety-like and depressive-like behaviour. This is supported by a rodent study showing that neurogenesis is required for spontaneous recovery from anhedonia, anxiety and cognitive flexibility impairments 4–6 weeks after exposure to chronic stress[137].

Reconciling memory, cognitive flexibility and mood disorders.

The role of neurogenesis in pattern separation and cognitive flexibility may have important implications for the above-described development of mood and anxiety disorders. During the encoding of a stressful or fearful experience, a memory engram of the fear-associated context is formed in the dentate gyrus. Once the stressor is over, cognitive flexibility is

required to learn that the same context has become safe and is now no longer associated with fear. This is often modelled by fear extinction paradigms in rodents, which have been suggested by some, but not all, studies to be dependent on neurogenesis[138] (but see also REF 84). To enable fear extinction or cognitive flexibility at the cellular level, adult-born neurons may inhibit the mature granule cells that had previously encoded the fear association and that contain the memory engram of the fearful situation. Inhibition of these granule cells would allow the erasure of the engram encoding the fearful association and, at the same time, would enable sparse activity for pattern separation during the encoding of the new safe association. If neurogenesis is impaired, a previously fear-associated memory engram may not be sufficiently cleared from the dentate gyrus and the new, safe condition may not be discretely encoded. As a result, the perception of fear will persist owing to a lack of neurogenesis and impaired cognitive flexibility. A lack of cognitive flexibility may then contribute to persistent HPA axis abnormalities and the engagement of stress and anxiety circuits, potentially leading to chronic psychopathology (FIG. 3). This effect may be particularly relevant from a clinical perspective, as cognitive flexibility is impaired across many psychiatric disorders, including post-traumatic stress disorder[139], obsessive–compulsive disorders[140] and depression[141]. Increasing neurogenesis may thus be a potential therapeutic strategy to facilitate reversal learning and cognitive flexibility as a treatment for patients with depression and anxiety disorders.

Therapeutic potential of neurogenesis

Neurogenesis mediates the behavioural effects of antidepressants.

Major support for the therapeutic potential of adult-born neurons originates from evidence that pharmacologically diverse antidepressants increase neurogenesis in rodents[117,142–144], non-human primates[122], human post-mortem brain tissue[26,145] and human hippocampal progenitor cells *in vitro*[146]. These neurogenic effects of antidepressants are most pronounced in the ventral dentate gyrus and are required for some of the behavioural effects of selective serotonin reuptake inhibitors (SSRIs) in rodents[25,115,116,127]. Non-pharmacological antidepressant strategies also potently increase neurogenesis and include interventions such as electroconvulsive shock therapy, environmental enrichment, physical exercise and calorific restriction[23,53,123,142,147,148]. Accordingly, neurogenesis is sufficient to confer antidepressant effects in chronically stressed mice[128,149] and to facilitate spontaneous remission from depression-like symptoms[137]. Enhancing neurogenesis through pharmacological or non-pharmacological means may thus be a promising strategy to confer stress resilience or antidepressant effects in patients. Indeed, physical (and mental) exercise has been shown to be effective in the treatment of clinical depression[150,151]. However, a limitation of this approach is that not all antidepressant effects are dependent on neurogenesis[117,127], and increasing neurogenesis is not always necessary to change behaviour[117,126,152]. Some pathological conditions, such as epilepsy, also increase neurogenesis, suggesting that an aberrant increase in neurogenesis may not always be beneficial[153,154].

Glucocorticoid-signalling or neurotrophic-signalling mechanisms that regulate neurogenesis have been identified in adult neural stem cells and young neurons[36,133,134,155–157]. However,

the clinical challenge remains to specifically target this defined population of adult-born cells pharmacologically. It is important to note in this context that the effects of SSRIs are, at least in part, mediated by serotonin 1A receptors (5HT1 ARs) that are located on mature granule cells but not on young adult-born neurons[158]. Whether these 5HTlAR-dependent effects of SSRIs are mediated by enhanced neurogenesis that results from the 5HT1AR-dependent release of neurotrophic factors from mature granule cells remains to be elucidated[158]. Of note, 5HT1ARs are G_i protein-coupled receptors that silence neuronal activity by opening G protein-coupled inward-rectifying potassium (GIRK) channels[159]. Therefore, it is possible that inhibiting dentate gyrus function may elicit antidepressant or anxiolytic effects, which is consistent with the proposed inhibitory role of young adult-born granule cells[69] (BOX 1). This assertion is also supported by a study showing that blocking GABA type A receptors in the ventral, but not in the dorsal, dentate prevents the anxiolytic effects of exercise[56]. Directly targeting the activity of mature granule cells may expand our therapeutic opportunities. Genes that are expressed specifically in the dentate gyrus may be promising candidate targets for novel drugs to confer such inhibitory effects (for examples, see REF. 160).

Neurogenesis and dentate gyrus impairments as targetable endophenotypes.

The heterogeneity of depression is a major impediment to the correct diagnosis and treatment of patients[161]. This heterogeneity complicates the identification of novel genes and brain circuits because the complexity of depressive symptomatology probably includes several different endophenotypes with distinct neurobiological impairments. Depression might be more correctly classified using a ‘bottom-up approach’ in which patients are diagnosed and treated based on discrete impairments of known neurobiological origin[162,163].

So far, no *in vivo* markers for neurogenesis in humans are available, although some promising tools are being developed. For example, magnetic resonance spectroscopy of the proton nuclear magnetic resonance peak at 1.28 ppm may prove useful for quantifying neural progenitor cells in the dentate gyrus[164]. Positron emission tomography markers, such as 3′-deoxy-3′-[^{18}F]fluorothymidine, which detects changes in cell proliferation, have recently been used in rodents and could potentially be translated into clinical applications[165,161]. Cerebral blood volume has been proposed as an indirect measure of human neurogenesis, as it is sensitive to changes in angiogenesis that may correlate with neurogenesis in the dentate gryus[167]. In addition to these *in vivo* approaches, *in vitro* strategies could use patient-specific human induced pluripotent stem cells to reprogramme patient-specific skin or hair cells to neurons that have granule cell-like phenotypes[168]. These granule cells could then be probed in culture for their ability to proliferate and differentiate or potentially grown as 3D hippocampal organoids[169], which may allow future drug screening for compounds with neurogenic potential on a patient-by-patient basis.

Identifying pattern separation and cognitive flexibility deficits in humans.

In addition to directly measuring levels of adult-born neurons, novel, neurogenesis-guided approaches could be aimed at identifying and treating dentate gyrus-dependent cognitive processes, such as pattern separation and cognitive flexibility, to determine the extent to which neurogenesis and dentate gyrus dysfunction contribute to disease manifestation.

In humans, neurocognitive testing, fMRI and *in vivo* hippocampal electrophysiological recordings have implicated the hippocampus in pattern separation. These studies have used hippocampal-dependent behavioural tasks that require discriminating small differences in highly similar object representations[170,171], emotional discrimination tasks[172], delayed match-to-sample tasks[49,77,102,173] and virtual-reality memory tasks with a spatial navigation component[174]. Indeed, performance in these tasks is impaired in individuals with depression who, as described above, may exhibit reduced levels of hippocampal neurogenesis[26,125,173,175–177]. Behaviour-based tests for hippocampal function and pattern separation may be useful to help guide diagnosis and to identify specific patients who would benefit from therapeutic interventions aimed at enhancing neurogenesis. For example, set-shifting tasks, in which attention needs to be redirected from a reinforced stimulus to a new stimulus, could probe cognitive flexibility[178,179]. Although performance in set shifting has primarily been linked to the PFC, some studies suggest that perseverative errors may also partly depend on the hippocampus[103,180–182]. We propose that, to distinguish dentate gyrus-dependent and PFC-dependent cognitive flexibility in humans, tasks will need to be designed that require the use of contextual or temporal cues to engage the hippocampus.

Tests for hippocampal function could potentially also include virtual-reality tasks that are modelled on rodent behavioural tests of pattern separation or reversal learning. For example, virtual radial arm mazes have already been used in some clinical studies and could assess pattern separation or reversal learning deficits with a similar design to those already used in rodent studies[77,183] (FIG. 4).

Treating pattern separation and cognitive flexibility deficits in humans.

Once patients have been classified on the basis of hippocampal pathology or hippocampus-dependent cognitive deficits, pharmacological interventions could include novel compounds, such as the anti-apoptotic and pro-neurogenic chemical P7C3, which has antidepressant effects in mice by increasing neurogenesis[149]. Similar compounds could also be developed to target dentate gyrus activity, as suggested above. Non-pharmacological strategies to increase neurogenesis should be informed by rodent studies, which have shown that neurogenesis can be enhanced by learning, aerobic exercise[53,150], environmental enrichment[23] and caloric restriction[148]. These strategies may indeed be useful therapeutic tools in humans to reduce anxiety disorders and depression. Novel therapeutic interventions could also target cognitive functions that are dependent on neurogenesis, such as reversal learning and cognitive flexibility, by using brain-training games that are designed to engage the hippocampus[184,185] (FIG. 4)

Conclusions and perspectives

The hippocampus has repeatedly been implicated in learning and memory, as well as in the behavioural response to stress and in the pathophysiology of mood disorders. These cognitive and mood-related functions of the hippocampus are not independent processes. Adult neurogenesis in the dentate gyrus has been proposed to regulate information processing in the hippocampus, and young neurons may contribute to the circuitry both by integrating new information and by inhibiting the activity of the dense network of mature

granule cells. This inhibitory effect of adult-born neurons may be important to erase previously established, fear-associated memories and to allow new, non-fear-associated memories to be formed instead (cognitive flexibility). At the same time, inhibition may facilitate sparse encoding of new information (pattern separation). Ultimately, memory clearance and sparse coding may reduce interference between the previous memory of a stressful or fearful context and the experience of a new safe context. Therefore, cognitive flexibility and pattern separation may be required to encode the novel context as safe and to facilitate recovery from anxiety and depressive symptoms by improving the ability to learn that the adverse context has changed.

In the clinic, identifying patients in whom dentate gyrus function and cognitive flexibility are impaired could be crucial to guide appropriate, individualized treatments. Indeed, increasing neurogenesis or enhancing cognitive flexibility may thus represent promising new treatment strategies for patients with compromised dentate gyrus function.

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Glossary

Cognitive flexibility
A cognitive process of executive function by which previously learned behavioural strategies can be modified to adapt to changes in environmental contingencies. Enables adaptation to new situations by switching from previously held beliefs or thoughts to new response strategies

Optogenetics
A research technique that allows the control of the activity of live neurons that have been genetically modified to express light-sensitive ion channels. Cell type-specific expression of photosensitive cation or anion channels can be used to acutely depolarize or hyperpolarize neurons with light in a spatially and temporally defined manner

Trisynaptic circuit
The flow of incoming information within the hippocampus generally occurs via three synapses: from entorhinal cortex to dentate gyrus, from dentate gyrus to CA3, and from CA3 to CA1

Critical period
The first 2–6 weeks in the development of adult-born neurons during which they display heightened excitability and plasticity

Input resistance
In a neuron, the ratio of the input voltage to the input current, as determined by the number of open membrane ion channels. Young adult-born neurons display high input resistance due to a low density of membrane K+ channels during early development

GABAergic inhibition
Inhibitory interneurons primarily release GABA, which activates ionotropic GABA type A receptors ($GABA_ARs$), or metabotropic $GABA_BRs$. $GABA_ARs$ are Cl^- channels that hyperpolarize mature neurons. In young adult-born neurons, $GABA_AR$-mediated currents are depolarizing because of a reverse Cl^- gradient.

Immediate early genes
Genes the expression of which is rapidly and transiently increased following neuronal activation; for example, *Fos*, *Arc* and *Zif268*. Such genes are used as markers for neuronal activity or to indelibly label neurons that are active during a specific experience

X-ray irradiation
Repeated exposure to 2.5–5 Gy of X-rays eliminates proliferating progenitor cells from the dentate gyrus and consequently ablates neurogenesis

Entorhinal cortex
A medial temporal lobe area that is divided into lateral and medial entorhinal cortices and that provides the main excitatory input into the hippocampal dentate gyrus

Hilar interneurons
Dentate gyrus interneurons are a diverse group of inhibitory neurons that are primarily located in the hilus and use GABA as their primary neurotransmitter.

Engrams
Neuronal ensembles that are recruited during memory encoding to form a cellular representation of that memory (memory trace)

Proactive interference
A neurobiological process by which previously learned information hinders the acquisition and distinct encoding of a new memory trace

Endophenotypes
Specific aspects of complex diseases that have a measurable biological foundation. Can be used to stratify heterogeneous (psychiatric) illnesses.

Negative affect
The experience of unpleasant emotions, poor self-confidence and lack of motivation

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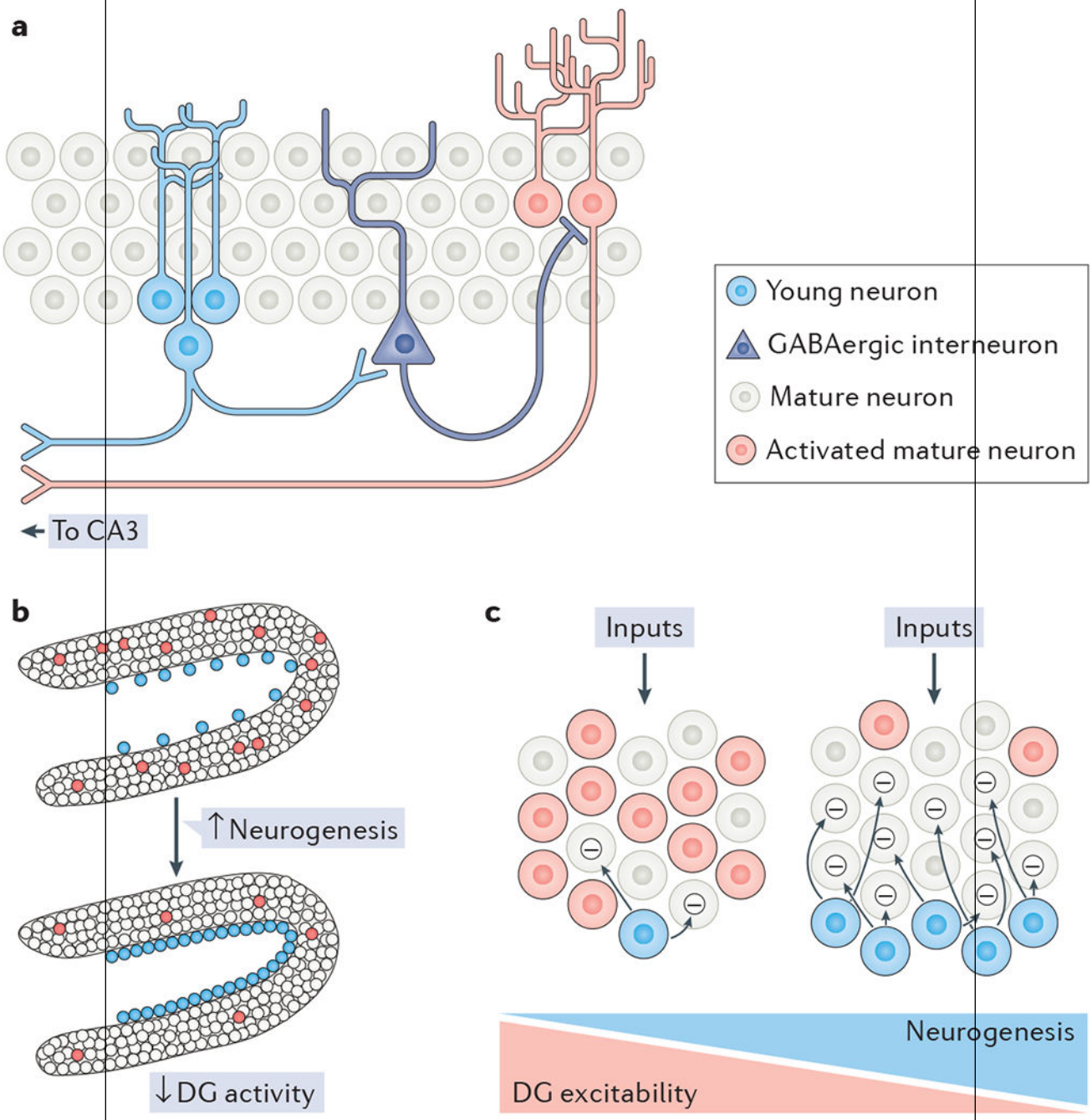
Box 1 |

The dentate gyrus inhibition hypothesis



Adult-born neurons functionally integrate into the rodent dentate gyrus (DG) at 2–3 weeks of age but require more than 8 weeks to develop electrophysiological properties that are similar to those of developmentally born, mature granule cells. At the microcircuit level, presynaptic terminals onto hilar interneurons develop at ~4 weeks of age and recruit feedback inhibition onto mature granule neurons[40,54] (see the figure, part

a). Accordingly, increasing neurogenesis in mice through environmental enrichment or transgenic strategies inhibits mature granule cells and reduces the overall excitability of the DG[68,69]. In line with this requirement for neurogenesis in DG inhibition, optogenetic stimulation of young neurons activates GABAergic interneurons in the hilus, and these interneurons in turn inhibit the dense population of mature cells *in vivo* and *in vitro*[69,70]. Conversely, ablation of neurogenesis reduces inhibitory input to granule cells, increases DG activity, enhances input–output coupling and expands the pool of active cells during reversal learning tasks[66,67] (see the figure, part **b**).

Pattern separation by the DG has been proposed to rely on sparse activation of the dense granule cell population. By inhibiting mature granule cells, adult-born neurons may decrease the activity of the DG during anxiogenic tasks and DG-dependent behaviours (see the figure, part **c**).

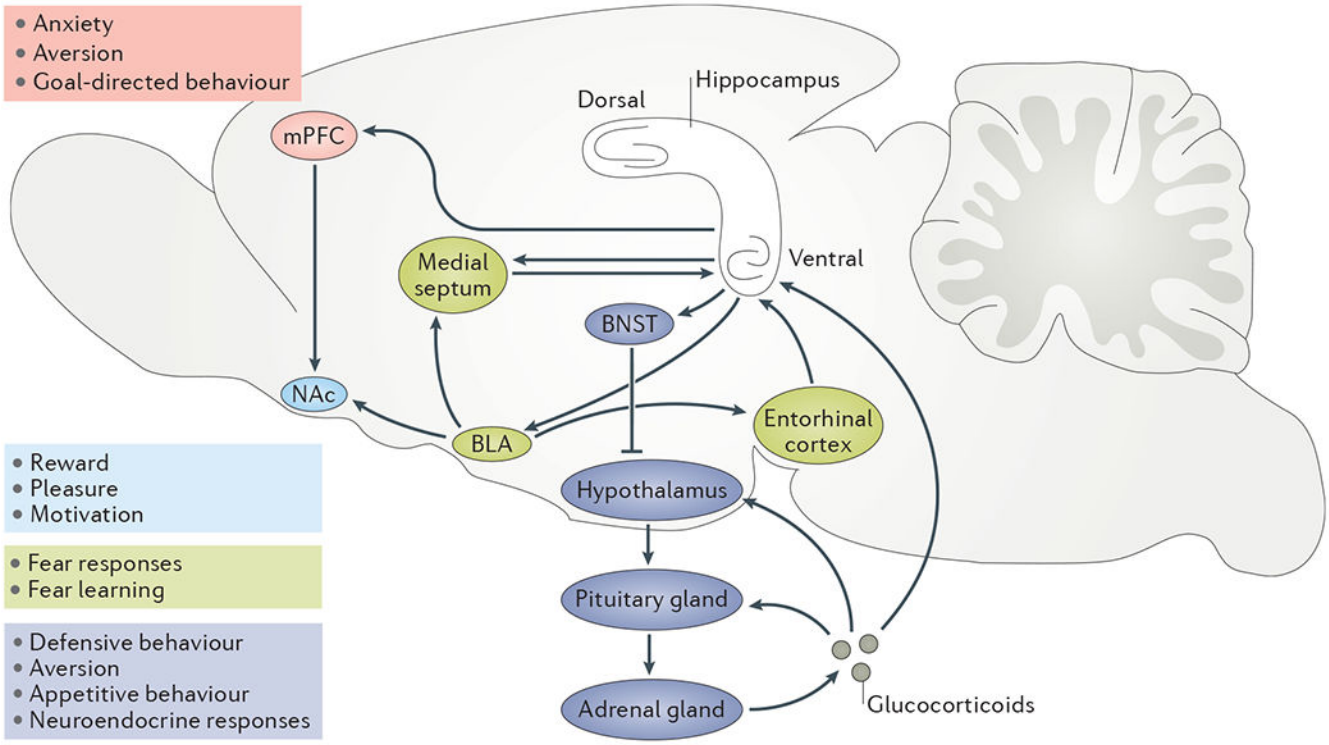


Figure 1 |. The ventral hippocampus and the neural circuitry of mood and anxiety.

The figure shows a simplified representation of the ventral hippocampus and its place within the circuits that are implicated in mood and anxiety. The basolateral amygdala (BLA) provides cholinergic input to the medial septum and glutamatergic input to the entorhinal cortex[186], which both send inputs to and can enhance ventral hippocampus activity to increase fear and anxiety-like responses[187]. Direct projections from CA1 in the ventral hippocampus provide feedforward inhibition by activating BLA interneurons[188]. The ventral hippocampus also sends glutamatergic project ions to GABAergic medium spiny neurons in the nucleus accumbens (NAc) to regulate NAc control over dopamine release from the ventral tegmental area (not shown). Ventral hippocampus-to-NAc projections promote reward-seeking behaviour in the absence of stress[31] but induce anxiety-like and depressive-like behaviour during stress[32]. Direct projections from the ventral hippocampus to the medial prefrontal cortex (mPFC) promote anxiety and stress susceptibility[29] and are also involved in antidepressant effects[32]. Glutamatergic projections from the ventral hippocampus activate GABAergic interneurons in the bed nucleus of the stria terminalis (BNST). These interneurons inhibit neurosecretory neurons in the paraventricular nucleus (PVN) of the hypothalamus. PVN neurons release corticotropin-releasing hormone, which stimulatesthe production of adreno-corticotropic hormone (ACTH) in the pituitary gland. ACTH stimulatesthe production and release of glucocorticoids from the adrenal cortex into the bloodstream. Glucocorticoids exert feedback inhibition on the hypothalamus–pituitary–adrenal axis by activating glucocorticoid and mineralocorticoid receptors in the pituitary gland, hypothalamus and hippocampus[34]. Consistently high levels of glucocorticoids during conditions of chronic stress can reduce hippocampal neurogenesis and cause neuronal atrophy[127,189].

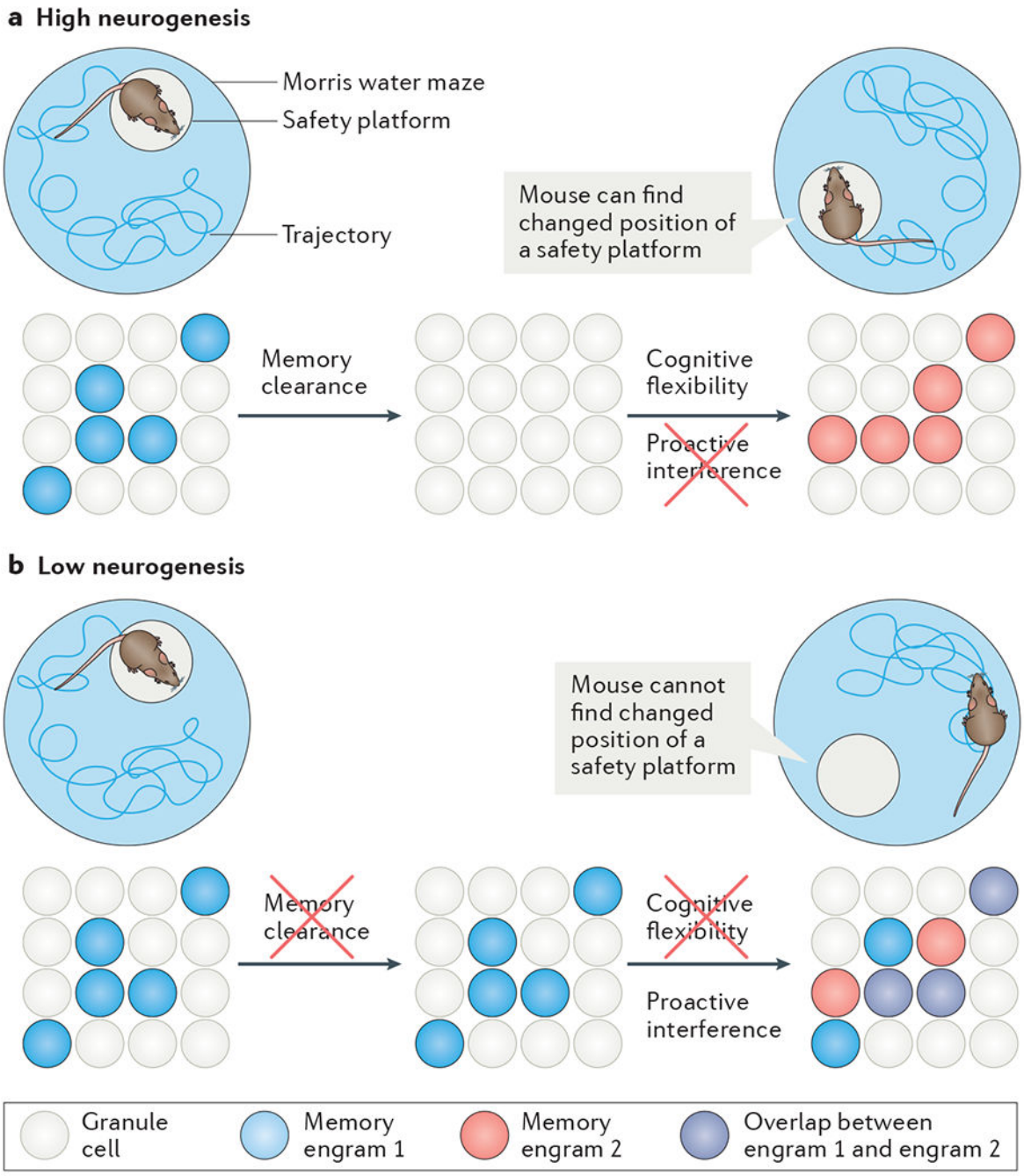


Figure 2 |. Neurogenesis facilitates cognitive flexibility by allowing the formation of new distinct memory traces.

Contextual memories, such as where a safety platform is hidden in a Morris water maze, are encoded by neuronal ensembles in the dentate gyrus. These cellular representations of a memory are known as memory traces or engrams.

a | With high neurogenesis, engrams may be cleared faster and transmitted to downstream processing structures. Efficient memory clearance reduces proactive interference between the memory of the previous location and the ability to accurately encode a novel location.

This may facilitate reversal learning and cognitive flexibility to promote the finding of a new safety platform once the location has been changed[101,105,106].

b | With low neurogenesis, engrams of previous contexts may not be cleared sufficiently. As a result, novel contextual contingencies may not be encoded appropriately by distinct neuronal ensembles. This may increase proactive interference, reduce cognitive flexibility and impair the ability to find the new location of a hidden safety platform.

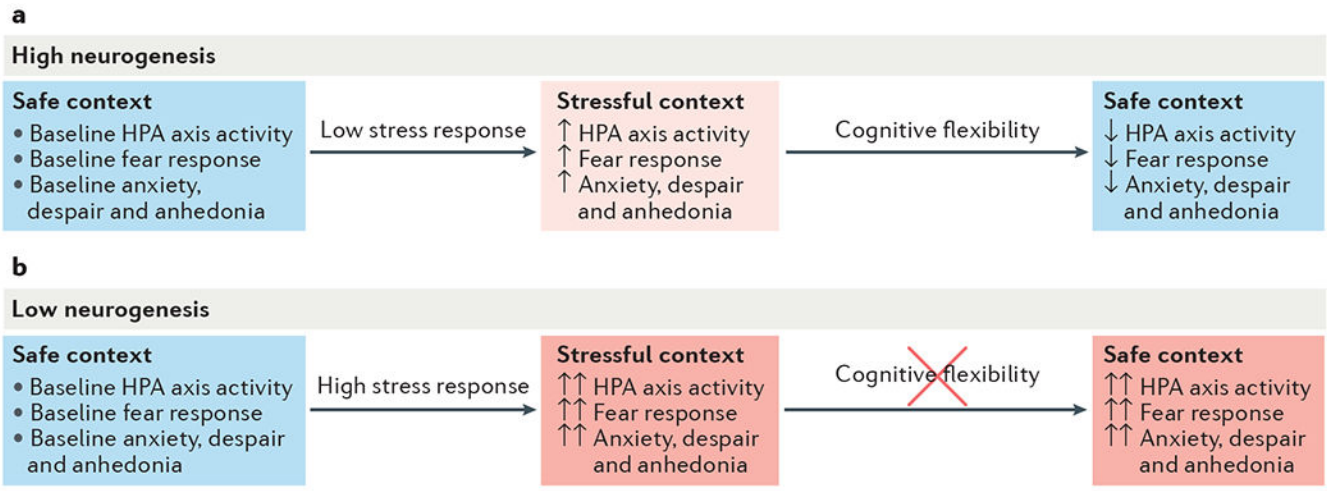


Figure 3 |. Neurogenesis promotes efficient stress recovery.

High or low levels of adult hippocampal neurogenesis do not influence baseline hypothalamus–pituitary–adrenal (HPA) axis activity, fear responses, innate anxiety, despair or anhedonia in rodents[84,115,128]. During stressful experiences, neuroendocrine responses and anxiety-like and depressive-like behaviour are less increased in mice with high levels of neurogenesis (part **a**) than in mice with low levels of neurogenesis[135,136] (part **b**). Once the stressor has ended, neurogenesis facilitates reversal learning and cognitive flexibility[137] to promote positive adaptation to novel, non-threatening environments. Therefore, increasing neurogenesis may facilitate fast recovery from HPA axis hyperactivity and anxiety-like and depressive-like behaviours and may prevent the development of chronic stress-induced psychopathology (part **a**).

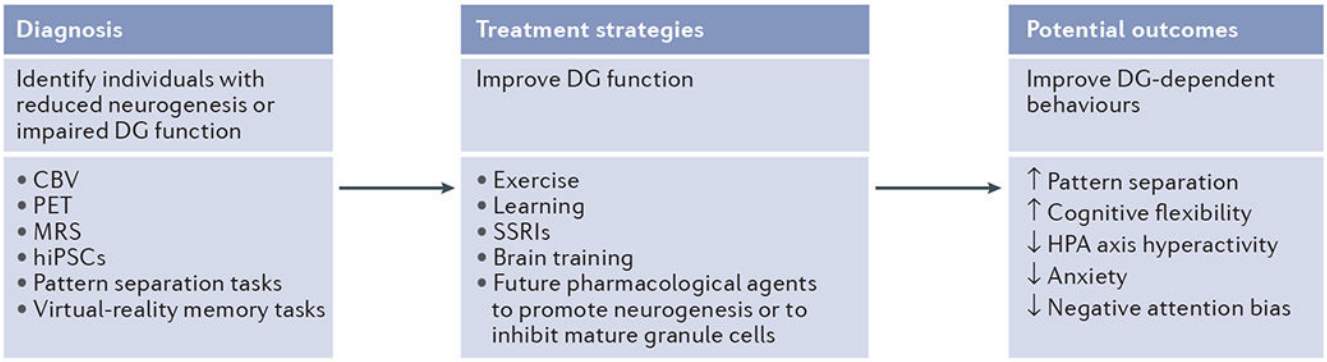


Figure 4 |. Potential methods of harnessing the function of adult-born neurons to treat dentate gyrus-dependent mood and anxiety disorders.

To harness adult hippocampal neurogenesis as a treatment for depression and anxiety, patients with reduced neurogenesis or patients with neurogenesis-dependent impairments in dentate gyrus (DG) function will first need to be identified (left panel). Possible diagnostic measures could include imaging technigues of cerebral blood volume (CBV) in the DG, which has been shown to correlate with levels of neurogenesis[167]; positron emission tomography (PET) using markers for neurogenesis that are currently being developed in mice[165]; and magnetic resonance spectroscopy (MRS) of the 1.28 ppm peak, which has been suggested to indicate levels of proliferating neural progenitor cells[164]. *In vitro* models, such as human induced pluripotent stem cells (hiPSCs), could be used to grow granule-like neurons from patient-specific skin or hair cells[168]. This may allow the testing of the effect of stress hormones or antidepressants on neurogenesis in culture[146]. Neurocognitive testing could also be used to identify patients with DG-dependent cognitive impairments. These tests could involve pattern separation tasks[170–172] or virtual-reality memory tasks[183] with a spatial navigation component, as patients with depression have an impaired performance in these tasks. Once patients with neurogenesis deficits or DG impairments have been identified, treatments could be used that have been shown to reliably increase neurogenesis in rodent models, such as exercise[53], learning-based approaches[23] and selective serotonin reuptake inhibitors (SSRIs)[142]. Cognitive strategies might include brain-training games, which have been shown to improve reversal learning and cognitive flexibility and to engage mood-relevant neural circuitry[184]. The development of future pharmacologicaltargets should be aimed at compoundsthat can increase neurogenesis orthat can inhibit mature granule cells and DG activity in patients. Enhancing neurogenesis and improving DG function in patients with confirmed impairments may increase cognitive flexibility and reduce hypothalamus–pituitary–adrenal (ElPA) axis hyperactivity, anxiety, negative attention bias and negative affect. Treating these impairments may facilitate efficient stress recovery and prevent or counteract the development of chronic psychopathology.