STRESS

Molecular mechanisms in the regulation of adult neurogenesis during stress

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Abstract | Coping with stress is fundamental for mental health, but understanding of the molecular neurobiology of stress is still in its infancy. Adult neurogenesis is well known to be regulated by stress, and conversely adult neurogenesis regulates stress responses. Recent studies in neurogenic cells indicate that molecular pathways activated by glucocorticoids, the main stress hormones, are modulated by crosstalk with other stress-relevant mechanisms, including inflammatory mediators, neurotrophic factors and morphogen signalling pathways. This Review discusses the pathways that are involved in this crosstalk and thus regulate this complex relationship between adult neurogenesis and stress.

Subgranular zone
(SGZ). A small region on the inner boundaries of the granular layer in the dentate gyrus of rodents. Cell proliferation of precursors to adult neurogenesis of granular neurons occurs in the SGZ.

Cell proliferation
Among the adult neurogenesis stages, this is an often-quantified stage of the process and is a measure of the number of new cells being formed in the subgranular zone that have the potential to become new neurons or glia.

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doi:10.1038/nrn3855

The emergence of adult neurogenesis as a research field in neuroscience has brought much excitement but also much scepticism. Technical limitations in studying the formation of new neurons in adulthood, particularly in humans, meant that initially there was little support for the idea that neurogenesis occurs on a scale that could have any relevance for brain function. However, recent observations from a cell-dating technique, which is based on a cold war-era spike in atmospheric ^{14}C levels and subsequent modelling, suggest that levels of adult neurogenesis remain substantial throughout life in humans[1,2]. This indicates that there are many more adult-born neurons than previously thought and that the various functions of the dentate gyrus probably involve adult-born neurons. This evidence has invigorated studies into the role of adult neurogenesis in health and behaviour. For example, some authors have theorized that the increased plasticity provided by developing neurons increases adaptive capacity in the face of change[3]. This theory gives an evolutionary significance to adult hippocampal neurogenesis, because an increased adaptive capacity has clear implications for survival in a challenging or stressful environment.

The hippocampus is primarily associated with forming and recalling memories, and spatial navigation. However, increasingly, it is also being associated with stress regulation and mood, possibly through the regulation of adult neurogenesis, although the putative mechanism through which this occurs, as discussed below, is still largely theoretical. Early studies of adult hippocampal neurogenesis in rodents have shown that stress could profoundly modulate adult neurogenesis in the subgranular zone (SGZ), which is the hippocampal neurogenic niche[4]. Since then, a large number of studies have confirmed this evidence. Moreover, more recent research has shown that, conversely, adult hippocampal neurogenesis can affect the regulation of the stress response, particularly in the context of animal models of chronic stress and depression. The identification of the molecular mechanisms underlying the modulation of neurogenesis that is seen during chronic stress and during the development of depression-like symptoms in animals may provide targets for the development of treatments for these conditions[4–6].

This Review first summarizes the mutual interaction between stress and adult neurogenesis and then examines several recent findings that shed light on the molecular mechanisms that are involved in the reciprocal regulation between the stress response and adult neurogenesis in the dentate gyrus.

Stress and adult neurogenesis interact

A large number of studies have shown that both acute and chronic stress affect adult neurogenesis, primarily cell proliferation, in several species[7]. For example, the acute psychosocial stressor of exposing tree shrews to a male of the same species decreases cell proliferation in the hippocampus[5]. In addition, acute exposure to fox odour transiently decreases hippocampal cell proliferation in rats, whereas non-threatening odours do not[8]. Chronic psychosocial stressors, such as repeated exposure to an intruder, have similar effects, including a sustained decrease in hippocampal cell proliferation and, in certain studies, a decrease in the levels of survival of newborn

Unpredictable mild stress
A rodent model of depression in which animals are exposed to repeated stressors that are deemed as mild in an order that cannot be predicted to avoid the development of habituation resilience.

Pattern separation
The process of reducing interference among similar inputs using non-overlapping representations.

Overgeneralization
In behaviour, this is the use of a few and/or non-representative experiences to make an inference of a current experience that is incorrect.

cells[9–12] in both shrews and rodents. Rodents exposed to chronic unpredictable mild stress, which is a commonly used model of depression, have decreased neurogenesis, show an impaired ability to further cope with stress over time and develop a depressive-like phenotype[13–15].

Importantly, an experimentally induced reduction in adult neurogenesis in the absence of stress does not, in general, induce depressive-like behaviour in rodents, which suggests that reduced neurogenesis precipitates depression-like symptoms by impairing stress modulation[16]. Indeed, recent studies have indicated that adult neurons can reduce the neuroendocrine stress responses and thus act as 'stress buffers' (REFS 17,18). In particular, these studies have demonstrated that reducing neurogenesis, through transgenic modifications or exposure to radiation, causes an increase in the levels of stress hormones following exposure to stress. Furthermore, these studies indicate a role of adult neurogenesis in enhancing glucocorticoid-mediated negative feedback on the hypothalamic–pituitary–adrenal (HPA) axis, as neurogenesis-deficient mice display a decreased suppression of glucocorticoids by dexamethasone.

Adult neurogenesis may also be involved in influencing whether events are perceived as stressful and may thus determine whether a stress response is elicited. In humans, this perception is dramatically changed during periods of chronic stress, such that events that are normally viewed as innocuous become aversive. The exact nature of this change remains elusive but is thought to involve a process known as pattern separation, by which specific events or stimuli are encoded into separate representations so that similar pieces of information can be distinguished in memory[4–6,19,20]. A loss of this ability, potentially through a decrease in adult neurogenesis, has been proposed to result in overgeneralization[21], in which numerous previous experiences have been encoded as being negative experiences, causing novel experiences to generally evoke negative memories. In addition to pattern separation, the buffering role of neurogenesis may cause changes in the perception of stress by increasing the malleability of contextual emotional processing, which enables the immediate differentiation between aversive and innocuous events (FIG. 1). A lack of neurogenesis could thus mean that even innocuous stimuli become emotionally negatively charged and induce a stress response in the absence of any objective danger — a tendency seen in individuals suffering from mood disorders.

The presence of adult neurogenesis and downstream mechanisms could therefore theoretically reduce stress responsiveness and essentially maintain resilience. Conversely, a dysfunction in these mechanisms may contribute to the risk of developing depression. Exactly how such a small number of cells could have such a potentially substantial effect is only beginning to be understood, although studies indicate that, during maturation, these new cells display unique properties that enable complex functions and have a huge impact on the network[22,23]. However, the currently available techniques have not yet allowed investigators to directly correlate these properties with mechanisms associated with emotional processes.

Importantly, despite the large amount of data showing a detrimental effect of stress on adult neurogenesis, the literature contains numerous studies in which stress has no effect or actually increases aspects of neurogenesis. Specifically, different acute stressors, such as footshock, immobilization and a novel environment, have been shown to increase cell proliferation in the dorsal dentate gyrus and to improve memory[24]. In addition, non-aversive activities that increase the levels of stress hormones, such as acute exercise and sexual experience, also increase adult neurogenesis in the rodent hippocampus[25,26]. These findings indicate that there is no simple, linear relationship between stress hormones and adult neurogenesis but that the relationship also depends on other factors. This opens the possibility that additional neurogenesis-modulating factors interact with stress-hormone-dependent molecular pathways, resulting in different effects depending on the molecular mechanisms involved — an idea that is explored below.

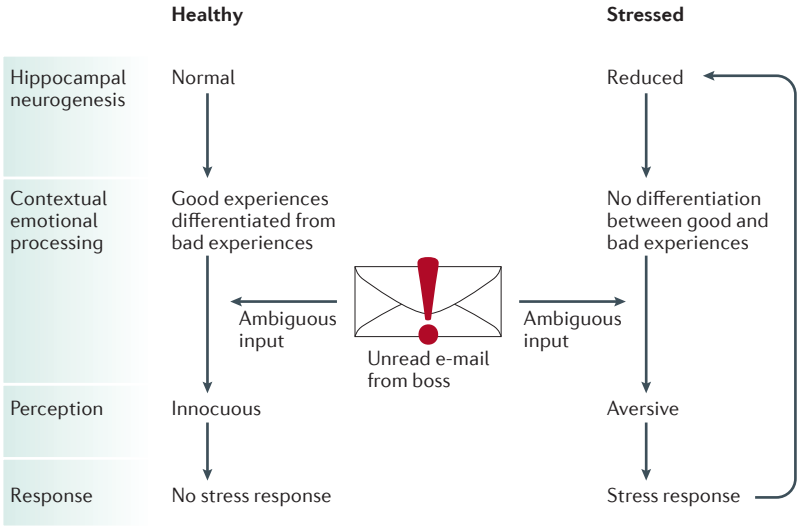


Figure 1 | **Theory of contextual emotional processing in stress perception.** A stress response begins with the perception of an event as being stressful, which is subjective. Perception, the result of processing of a novel event (exemplified here by an unread work-related e-mail), may involve using the emotional valence of similar experiences from the past to put the novel event into context with an assigned emotional valence. This process of putting a novel experience into an emotional context ('contextual emotional processing') may utilize the unique 'malleable' architecture of the hippocampal formation, including the properties of immature neurons in subregions of the dentate gyrus, to utilize a range of existing circuits in order to assign valence to the novel experience. Despite previous negative experiences that are emotionally charged, a healthy level of neurogenesis could theoretically create malleability during contextual emotional processing, allowing this event to be processed as a separate event that is encoded with its own valence. The perception of this novel event is thus innocuous and no stress response is initiated. However, during chronic stress, decreased levels of neurogenesis may reduce the malleability of contextual emotional processing. In the absence of malleability, an increased sensitivity to danger may mean that memories with negative valence are more readily recalled during contextual emotional processing, and thus novel events are more easily assigned a negative valence. In the example shown, a chronically stressed individual receiving an innocuous e-mail may therefore have a diminished ability to differentiate past emotionally charged negative experiences (e-mails with negative connotations) from the present event. The perception of the event is therefore aversive, and a stress response is induced. Stress can cause a decrease in adult neurogenesis that may propagate further decreases in malleability in contextual emotional processing, leading to a negative cycle.

Glucocorticoid signalling mechanisms

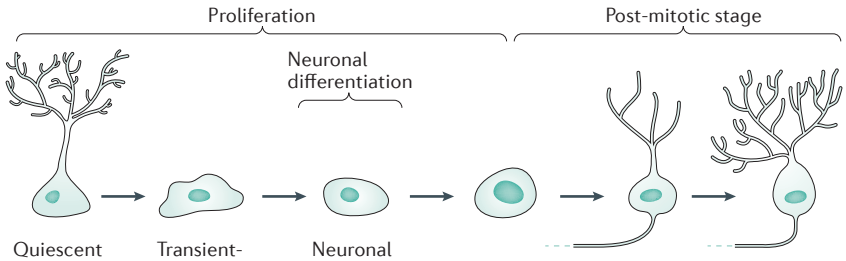
Glucocorticoids and glucocorticoid receptors. Aversive events initiate an acute stress response that activates the HPA axis and culminates in the release of glucocorticoid hormones from the adrenal cortex: namely, cortisol in humans and corticosterone in rodents[27]. Glucocorticoids cross the blood–brain barrier and target mineralocorticoid receptors and glucocorticoid receptors in many brain areas, including the hippocampus, where adult neurogenesis occurs.

Mineralocorticoid receptors and glucocorticoid receptors are found in the cytoplasm, but after ligand binding they translocate to the nucleus and then form either homo- or heterodimers that interact with DNA and thereby cause transactivation or trans-repression of specific genes. This may be one way in which stress-induced glucocorticoids and their receptors regulate adult neurogenesis (see below). Indeed, although early studies reported that neurogenic cells begin to express mineralocorticoid receptors and glucocorticoid receptors 4 weeks after proliferation, subsequent studies using more advanced imaging techniques found that glucocorticoid receptors are expressed much earlier[28,29]. Specifically, a large majority of quiescent neural progenitors (type 1) and amplifying progenitors (type 2a) express glucocorticoid receptors (FIG. 2). Interestingly, the expression of glucocorticoid receptors ceases concomitantly with the expression of the immature neuronal marker doublecortin in intermediate progenitors (type 2b). The expression resumes briefly when these cells become neuroblasts (type 3), and glucocorticoid receptors are fully expressed once the cells become mature. The expression of glucocorticoid receptors in dividing hippocampal cells suggests that glucocorticoids can influence these dividing cells and thus neurogenesis.

Initial studies using systemic corticosterone injections in rodents showed the ability of glucocorticoids to affect adult neurogenesis by inhibiting cell proliferation, cell differentiation and cell survival[4,30–32]. Similarly, in human hippocampus-derived stem cells treated *in vitro*, cortisol reduced both proliferation and differentiation[33]. Further studies showed that the inhibitory effects of stress or corticosterone treatment on adult neurogenesis in rodents are mainly dependent on glucocorticoid receptors[34–37]. However, *in vitro* experiments using mineralocorticoid receptor or glucocorticoid receptor antagonists in human cells have demonstrated that both types of receptor regulate adult neurogenesis but in opposite directions: low and high cortisol levels induce a mineralocorticoid receptor-dependent increase and a glucocorticoid receptor-dependent decrease in cell proliferation, respectively[38]. In addition, a recent animal study, in which lentiviral techniques were used to knock down glucocorticoid receptors in the SGZ of mice[39], shows that new neurons display accelerated neuronal differentiation and migration, and have more developed axons and dendrites, suggesting that glucocorticoids inhibit these aspects of adult neurogenesis by binding to these receptors.

In summary, during stress, the different stages of adult neurogenesis are regulated by glucocorticoids acting mainly through glucocorticoid receptors. These receptors can function as transcriptional activators or repressors and thus regulate gene transcription in dividing cells (as discussed below). It remains to be determined whether glucocorticoids have indirect effects on hippocampal neurogenesis: for example, by affecting glia, interneurons and/or vascular tone.

Regulation of gene transcription. Several studies have aimed to identify genes that are modulated as a result of stimulation of glucocorticoid receptors by glucocorticoids. In one such study, human hippocampal progenitor cells *in vitro*[38] were treated with high levels of cortisol during the proliferation phase. Pathway analysis of gene transcription revealed numerous signalling pathways that were affected



	Quiescent neural progenitor	Transient-amplifying cell	Neuronal progenitor cell	Neuroblast	Immature neuron	Mature neuron
GR expression (% cells)	50–80%	50–80%	0%	50%	0–10%	100%
MR expression (% cells)	0%	0%	0%	0%	0–50%	100%

Figure 2 | **Expression of glucocorticoid receptors and mineralocorticoid receptors during hippocampal neurogenesis in mice.** The expression of glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) varies during the different stages of neuronal development. In mice, GRs are expressed in the majority of neuronal developmental stages, although not during neuronal differentiation; all mature neurons express GRs, whereas the percentage of GR-expressing cells in earlier stages varies. MRs are expressed only in the last stage of neuronal development in mice, and all mature neurons express MRs. Less data exist regarding the expression of MRs and GRs in neuronal development in humans, but both GRs and MRs are expressed in undifferentiated cells as well as mature neurons (not shown). Adapted with permission from REF. 29, Copyright © 2004 John Wiley & Sons.

Contextual emotional processing
The process of putting a novel experience into an emotional context using the emotional valence of similar previous experiences.

Dorsal dentate gyrus
A region that is thought to be associated with spatial memory processing.

Cell differentiation
A quantifiable stage of adult neurogenesis in which the number of cells fated to become neurons can be measured.

by this treatment. These included three pathways that are well known to regulate adult neurogenesis: namely, the forkhead box protein O3 (FOXO3A) pathway, which is activated; and the transforming growth factor-β (TGFβ)–SMAD2–SMAD3 pathway and the Hedgehog pathway, which are inhibited[38,40–44]. Interestingly, gene transcription and subsequent pathway analyses of hippocampal tissue from a rodent prenatal stress model yielded similar results, including decreases in Hedgehog and TGFβ–SMAD2–SMAD3 signalling and a reduction in the signalling of nuclear factor-κB (NF-κB), a pro-inflammatory transcription factor[38]. Although *in vitro* and *in vivo* comparisons should be made with caution, the consistency of findings between a human neuronal cell line and the rodent hippocampus indicates that these pathways are likely to be very important in the regulation of neurogenesis by glucocorticoids. In addition, through the use of this human hippocampal progenitor cell line, the glucocorticoid receptor-regulated gene serum/glucocorticoid-regulated kinase 1 (*SGK1*) has been found to be involved in cortisol-induced decreases in neurogenesis (see below for crosstalk mechanisms involving SGK1)[45].

Another rodent study identified several changes in gene expression in the whole dentate gyrus after chronic mild stress, including a decrease in the level of the co-regulator CBP (cyclic AMP-responsive element-binding protein (CREB)-binding protein). This decrease was reversed by treatment of animals with a glucocorticoid receptor antagonist, again implicating the glucocorticoid receptor in these molecular changes[46]. Pathway analysis of these gene expression data also identified stress-induced, glucocorticoid receptor-dependent changes in the expression of several genes involved in neurogenesis, including disabled 1 (*Dab1*), FYN proto-oncogene (*Fyn*) and myocyte enhancer factor 2A (*Mef2a*)[47–49]. This study also found changes in the expression of groups of genes involved in calcium signalling and cytokine expression, both of which are known to regulate adult neurogenesis[50,51].

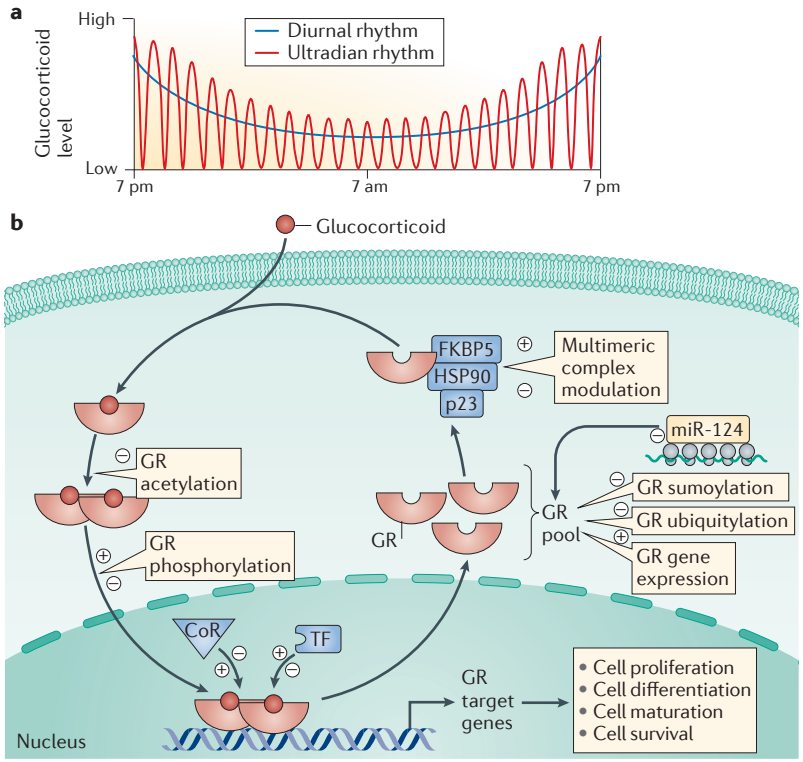


Figure 3 | **Modulation of glucocorticoid and glucocorticoid receptor activity.** Glucocorticoid levels and glucocorticoid signalling are modulated through many different mechanisms. **a** | The daily glucocorticoid rhythm (the diurnal rhythm) varies greatly throughout the day (blue line), peaking at the beginning of the active phase (exemplified here in rats, but it is generally similar across species). The diurnal rhythm is an average of the ultradian rhythm (red line), which has a much larger variation that is created by hourly glucocorticoid pulses[125]. **b** | The glucocorticoid receptor (GR) is found as part of a large multimeric protein complex and, once glucocorticoids bind, it can be released from this complex; this is also dependent on the multimeric complex proteins and their modulation. Glucocorticoid-bound GRs form hetero- or homodimers that, once translocated into the nucleus, interact with DNA to control gene transcription. Once the GR has bound to the DNA, it can be released and shuttled out of the nucleus to be recycled and reform part of the multimeric complex. These GR dynamics, which are determined in part by ultradian pulsing, may be important for gene regulation. This cycle can be modulated by various processes at different stages. For example, acetylation of the GR affects its ability to form dimers and interact with transcription factors (TFs), and phosphorylation modulates the ability of glucocorticoids to bind to and shuttle the receptor into or out of the nucleus. TFs (such as nuclear factor-κB (NF-κB)) interact with GR-forming heterodimers and modulate gene expression; co-regulators (CoRs), of which there are many different types, including subgroups of co-activators and co-repressors, modulate GRs through different mechanisms, often by modifying interactions with other TFs. Finally, the number of GRs available (the GR pool) is very important for the magnitude of transcriptional effects on adult neurogenesis, and this can be modified at the mRNA level by microRNA-mediated gene silencing or at the protein level by ubiquitylation and sumoylation, which result in GR degradation in the proteasome. In addition, sumoylation inhibits protein–protein interactions, such as dimerization. These numerous mechanisms exemplify the many ways in which other pathways can, through crosstalk, modify GR signalling. FKBP5, FK506-binding protein 5; HSP90, heat shock protein 90; miR-124, microRNA-124.

Glucocorticoid levels. Endogenous glucocorticoid levels display both circadian rhythms and ultradian rhythms, with superimposed stress-induced increases in these levels. Ultradian rhythms consist of sharp pulsatile peaks and troughs occurring roughly every hour and are intercalated with circadian rhythms, which themselves are determined by the average amplitude of the ultradian pulses[52–54] (FIG. 3). The ultradian oscillations in glucocorticoid levels — and the associated patterns of glucocorticoid binding to and dissociation from glucocorticoid receptors — regulate gene expression. This role of ultradian rhythms in the regulation of gene expression suggests that glucocorticoid pulsatility may be involved in maintaining the transcriptional activity that is necessary to sustain normal levels of adult neurogenesis. Indeed, the circadian diurnal rhythm in corticosterone levels is necessary for antidepressants to increase adult neurogenesis in rats and potentially to regulate the baseline levels of adult neurogenesis[55]. Whether acute or chronic stress influences these rhythms, and the related glucocorticoid receptor-mediated gene transcription, is not well understood, but it has been proposed that ultradian rhythms have a role in the normal, acute stress response and in its disruption during chronic stress[56–58]. The potential importance of these factors in the mechanism by which stress induces changes in neurogenesis remains a pressing question.

Glucocorticoid receptor modifications. The transcriptional activity of glucocorticoid receptors is also dependent on the amount of glucocorticoid receptor protein, which can be modulated by changes in gene expression, protein degradation and post-translational modifications, such as ubiquitylation, acetylation, sumoylation and phosphorylation (FIG. 3). Increases in glucocorticoid levels during acute and chronic stress are associated with changes in glucocorticoid receptor expression in the rodent hippocampus, specifically with a decrease in glucocorticoid receptor expression and an increase in the ratio of nuclear-to-cytosolic protein levels[59,60]. Human hippocampal progenitor cells also show increases in the ratio of nuclear-to-cytosolic glucocorticoid receptor levels during chronic cortisol exposure, indicating that these changes occur specifically in cells that are capable of adult neurogenesis[45].

The regulation of glucocorticoid receptor protein expression levels also occurs through microRNA-mediated gene silencing, such as by microRNA-124 (miR-124). Interestingly, the induction of miR-124 is crucial for the initiation of neuronal differentiation in the subventricular zone (SVZ), from where adult-born neurons migrate to the olfactory bulb[61]. miR-124 is also expressed in the hippocampus, where it downregulates glucocorticoid receptor protein levels and, consequently, the transcription of glucocorticoid receptor-regulated genes[62]. Considering the absence of glucocorticoid receptor expression in intermediate progenitor cells in the SGZ, as mentioned above[28,29], it could be speculated that an orchestrated absence of glucocorticoid receptors, owing to miR-124-mediated silencing of glucocorticoid receptor expression, induces the gene expression changes that are necessary for the differentiation of cells in this region. Another microRNA, miR-18, has been shown to reduce glucocorticoid receptor protein expression in the paraventricular nucleus during stress[63], indicating that microRNA-mediated gene silencing is a mechanism through which stress decreases glucocorticoid receptor gene transcription in multiple areas of the brain and thus possibly alters aspects of adult neurogenesis.

Glucocorticoid receptor protein levels are also regulated through degradation of these receptors. Proteasome-mediated degradation, in part through ubiquitylation, has been suggested to affect glucocorticoid receptor-mediated gene transcription during stress[64,65]. Deletion of the ubiquitin-mediating gene ubiquitin protein ligase E3A (*Ube3a*), which encodes the protein involved in targeting proteins for their multi-ubiquitylation, has also been shown to decrease neuronal differentiation during adult neurogenesis, although the mechanism remains unknown[66]. However, another study showed that dysfunction of UBE3A decreased ubiquitin-mediated glucocorticoid receptor degradation and that this may be the mechanism through which such dysfunction induces an anxiety-like phenotype[67]; in turn, anxiety-like phenotypes have been associated with a decrease in adult neurogenesis. These studies indicate that ubiquitylation may be important in the regulation of both stress and adult neurogenesis.

Acetylation and deacetylation of the lysine residues within the glucocorticoid receptor can also affect its transcriptional activity. For example *in vitro* data show that deacetylation of glucocorticoid receptors by histone deacetylase 2 (HDAC2) during glucocorticoid stimulation of macrophage cells is necessary for the interactions of these receptors with NF-κB and the subsequent repression of downstream targets[68]. NF-κB has been implicated in stress-induced impairment of neurogenesis[69], and therefore it is possible that the acetylation state of glucocorticoid receptors may be similarly important in neurogenic cells for the interaction of these receptors with NF-κB during stress. Sumoylation, similarly to ubiquitylation, is a process by which peptides are attached to proteins, causing, among other outcomes, inhibition of protein–protein interactions. Studies show that sumoylation of glucocorticoid receptors leads to inhibition of transcriptional activity and promotes the degradation of these receptors[70–72].

Phosphorylation and/or dephosphorylation of glucocorticoid receptors can induce changes in the stability of glucocorticoid receptors and thereby modulate their transcriptional activity, subcellular localization and interaction with other proteins[73–76]. In fact, the glucocorticoid receptor has to be phosphorylated for glucocorticoids to bind to it, and glucocorticoid binding induces additional phosphorylation of the receptor[77,78]. In a study in rats, both acutely stressed and chronically stressed animals displayed similar glucocorticoid receptor-mediated transcriptional changes in the hippocampus. The glucocorticoid levels in the acutely stressed rats were fivefold higher than they were in control rats, as expected during a stress response eliciting transcriptional change; however, the glucocorticoid levels in chronically stressed rats were unexpectedly lower than those in control rats[79]. Glucocorticoid receptor-mediated transcriptional activity in these chronically stressed animals was shown to be due to changes in the phosphorylation of these receptors in the nucleus, which exhibited a distinct phosphorylation profile that enabled their continued activity despite the lack of ligands. These results are remarkably consistent with findings from an *in vitro* study in the aforementioned human neuronal progenitor cells[45], which also showed that glucocorticoid-induced glucocorticoid receptor-mediated transcriptional activity was dependent on the phosphorylation state of the receptor[45] and that transcriptional activity could potentially continue even in the absence of the initial glucocorticoid stimulus. In particular, glucocorticoid-mediated decreases in cell proliferation and neuronal differentiation resulted from a kinase-mediated increase in the phosphorylation of glucocorticoid receptors, in this case by SGK1 (REF. 45). This study explicitly exemplifies how post-translational modifications have direct consequences on the molecular mechanisms by which stress-induced changes in glucocorticoid levels regulate adult neurogenesis.

Glucocorticoid receptor protein–protein interactions. When not associated with glucocorticoids, glucocorticoid receptors are predominantly found in the cytoplasm as part of a multimeric molecular chaperone complex that includes several heat shock proteins (HSPs), such

Circadian rhythms
In terms of hormone secretion, these rhythms vary throughout the day and comprise a period in which there is generally a high level of hormone secretion and a period in which a generally lower level of hormone is secreted.

Ultradian rhythms
In terms of hormone secretion, these rhythms vary within circadian rhythms and are composed of roughly hourly pulses of hormone release that result in peaks in hormone levels followed by troughs in which the hormone is broken down.

Subventricular zone
(SVZ). A thin strip composed of several layers on the inner walls of the lateral ventricles of the rodent forebrain. Cell proliferation of precursors to adult neurogenesis of mainly olfactory bulb neurons occurs in the SVZ.

as HSP70 and HSP90, the HSP90-binding protein p23 (also known as PTGES3) and proteins that help to bind HSP90 such as FK506-binding protein 5 (FKBP5), FKBP4, cyclophilin 40 (also known as PPID), carboxyl terminus of HSP70-interacting protein (CHIP) and, in some circumstances, the phosphatase PP5. Once glucocorticoids bind to the glucocorticoid receptor within this complex, a conformational change releases a large part of the complex in preparation for glucocorticoid receptor translocation to the nucleus[80]. The large numbers of proteins in this complex all have the potential to modulate glucocorticoid receptor activity. Interestingly, like the glucocorticoid receptor, some of the proteins in this complex may undergo post-translational modifications during stress, ultimately modulating glucocorticoid receptor-mediated transcriptional activity. For example, chronically stressed rats have upregulated levels of the chaperone complex protein FKBP5 in the ventral dentate gyrus of the hippocampus and in the cortex, together with a decrease in glucocorticoid receptor phosphorylation in the cortex[60]. Furthermore, HSP90 inhibits glucocorticoid receptor–DNA interactions in the nucleus[81] and is crucially involved in the regulation of the pulsatile glucocorticoid receptor response to the glucocorticoid ultradian rhythm[82]. The ability of these proteins to influence glucocorticoid receptor function during stress indicates that they are likely to affect adult neurogenesis, although no studies have specifically examined this hypothesis.

In the nucleus, glucocorticoid receptors can also interact with the transcription factors that are involved in the modulation of adult neurogenesis during stress, such as NF-κB and CREB, to rapidly repress gene transcription[46,69]. Co-regulators (which include co-activators and co-repressors) form part of multiprotein complexes, primarily within the nucleus, which modulate glucocorticoid receptor-mediated transcriptional activity, often in combination with transcription factors. Like the glucocorticoid receptor itself, co-regulators can undergo post-translational modifications and thus can similarly be dynamically regulated by other signalling pathways[83]. Although data are limited, studies have indicated that aspects of stress are modulated by numerous co-regulators, including the 160 steroid receptor co-activators, such as steroid receptor co-activator 1 (SRC1; also known as nuclear receptor co-activator 1), SRC2, SRC3 and CBP, as well as histone acetyltransferase p300, all of which regulate glucocorticoid receptors[84]. Currently, no co-regulators have been identified intrinsically in neurogenic cells but, as glucocorticoid receptor transcriptional activity is regulated by these mechanisms, it is probable that they are involved in the glucocorticoid receptor-regulated changes in neurogenesis during stress.

Cytokines

Glucocorticoids are not the only factors released during stress. For example, psychological stress in humans initiates an acute catecholamine response that results in the release of pro-inflammatory cytokines in the periphery, from mononuclear cells[85]. Although cytokines that are produced in the periphery do not readily cross the blood–brain barrier, there are several mechanisms by which peripheral inflammation can change brain function and behaviour[86]. In addition, rodent studies have shown that stress also induces a catecholamine-mediated release of pro-inflammatory cytokines in several regions of the brain, including the hippocampus, where interleukin-1β (IL-1β) levels are increased through a noradrenaline-mediated mechanism[87]. Regulation of the inflammatory response by stress is further exemplified by changes in the immune response during chronic stress, in which there is a complex dynamic between inflammation, glucocorticoids and the HPA axis, but this is beyond the scope of this Review[88]. However, the literature indicates that chronic stress, in humans and in animals, induces an increased inflammatory state in the periphery and in the brain, potentially as a result of a blunting of glucocorticoid inhibitor effects on the immune response[89–91].

In animal models, changes in the inflammatory state that are induced by chronic stress negatively correlate with changes in adult neurogenesis[91]. For example, chronic stress increases IL-1β and IL-6 levels in the hippocampus, which then correlate with decreases in adult neurogenesis[50,91]. The decrease in adult neurogenesis is due to a decrease in cell proliferation mediated by IL-1β and its receptor, IL-1R1 (IL-1 receptor type 1), which is expressed in neuronal stem cells and progenitor cells, as well as immature and mature adult-born neurons[50,69]. IL-1β also decreases neuronal differentiation of human and rat hippocampus-derived stem cells *in vitro*[92,93]. However, chronic intra-hippocampal IL-1β administration has also been found to increase cell proliferation in mice and, with prolonged treatment, in human hippocampal stem cells *in vitro*[92,94]. These contradictory findings indicate that additional molecular pathways are involved. For example, NF-κB signalling is involved in the stress-induced decrease in proliferation of stem cells (but not progenitor cells) in the hippocampus, and the induction of NF-κB signalling is blocked by pretreatment with an IL-1R1 antagonist[69], indicating that the inhibition of neurogenesis by stress is mediated, at least in part, by IL-1β stimulation of NF-κB signalling. The involvement of further pathways is exemplified in human cells, in which IL-1β affects the kynurenine pathway and specifically increases the levels of neurotoxic metabolites, whereas inhibition of this pathway *in vitro* ameliorates IL-1β-induced decreases in neurogenesis[92]. Furthermore, IL-1β-induced decreases in cell proliferation and neuronal differentiation in stem cells are ameliorated by pharmacological inhibition of glycogen synthase kinase 3β (GSK3β) activity[93], indicating that the GSK3β signalling pathway is also involved in mediating the effects of IL-1β on adult neurogenesis.

Neurotrophic factors

Neurotrophic factors are important for the growth and survival of developing neurons and for the maintenance of mature neurons. It is therefore not surprising that they have an important role in the regulation of adult neurogenesis. Interestingly, stress influences the levels of several neurotrophic factors in the brain, including brain-derived

Ventral dentate gyrus
A region that is thought to be associated with emotional memory processing.

neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and neuregulin 1 (NRG1), which is part of the epidermal growth factor family of proteins[95].

Studies have shown that stress, depression and adult neurogenesis are all associated with changes in BDNF levels, although how BDNF may affect these is not straightforward. For example, acute stress decreases BDNF mRNA and protein levels in the hippocampus, but these changes are transient, indicating that BDNF levels vary greatly with regards to the timing of stress[96]. The effects of BDNF on adult neurogenesis are equally complex. To begin with, the high-affinity BDNF receptor TRKB (tropomyosin-related kinase B; also known as NTRK2) is expressed in the hippocampus in stem and maturing cells, whereas the low-affinity receptor p75 is expressed in proliferating cells[97]. Furthermore, there are many contradictions regarding the effects of BDNF on adult neurogenesis: some studies indicate that there are no effects of BDNF on cell proliferation and survival, whereas others indicate positive effects on these processes These discrepancies, along with data showing that BDNF modulates other neurogenesis-related factors such as VEGF and glucocorticoids, indicate that the effects of BDNF on neurogenesis may be indirect[98]. Indeed, a recent study has shown that BDNF promotes differentiation and maturation of adult-born neurons indirectly by enhancing the release of GABA from interneurons[99].

Several studies have shown a decrease in VEGF levels in the hippocampus of rats in response to both chronic and acute stress, whereas other studies, including both rat and mouse studies, have found no change in the level of this growth factor[100]. The majority of studies report that VEGF increases cell proliferation through the activation of VEGF receptor 2 (also known as FLK1), which is expressed in neural progenitors and induces CREB signalling[101–104].

It is not known whether NRG1 has a role in stress-mediated regulation of adult neurogenesis. However, in NRG1-mutant mice that are heterozygous for a mutation affecting the transmembrane domain of NRG1, changes in HPA axis regulation occur in the form of an increased basal level of glucocorticoids and changes in glucocorticoid receptor expression in several brain regions[105]. Furthermore, direct injection of NRG1 increases cell proliferation in the dentate gyrus of mice through potential cell-intrinsic ERBB3 receptors[106], suggesting that such a role for NRG1 may exist.

Morphogen signalling pathways

Morphogens regulate the early stages of adult neurogenesis; specifically, they regulate the maintenance, activation and fate choice of adult neural precursors[107]. Recent evidence has indicated the involvement of sonic hedgehog (SHH) and wingless (WNT) pathways during stress.

The signalling protein SHH is important for initiating the proliferation of neurogenic cells within the dentate gyrus[108]. Both quiescent neural stem cells and transient-amplifying progenitors have been shown to proliferate in response to SHH signalling[43]. This response is crucial for the maintenance of the neurogenic pool in the adult brain and is dependent on different components of the SHH signalling pathway, including the SHH receptor Patched (PTCH), a PTCH-associated G protein-coupled transmembrane protein called Smoothened (SMO), with which PTCH forms a complex, and the GLI family of transcription factors[108,109]. Of note, the role of GLI proteins in adult neurogenesis has so far only been examined in the SVZ, where the precise coordination of the expression of these proteins is critical for the maintenance of stem cell populations[110]. Recently, SHH signalling was shown to be involved downstream of glucocorticoid stimulation of neural progenitors, ultimately resulting in a decrease in cell proliferation; this suggests a role for SHH in stress-induced changes in adult neurogenesis[38].

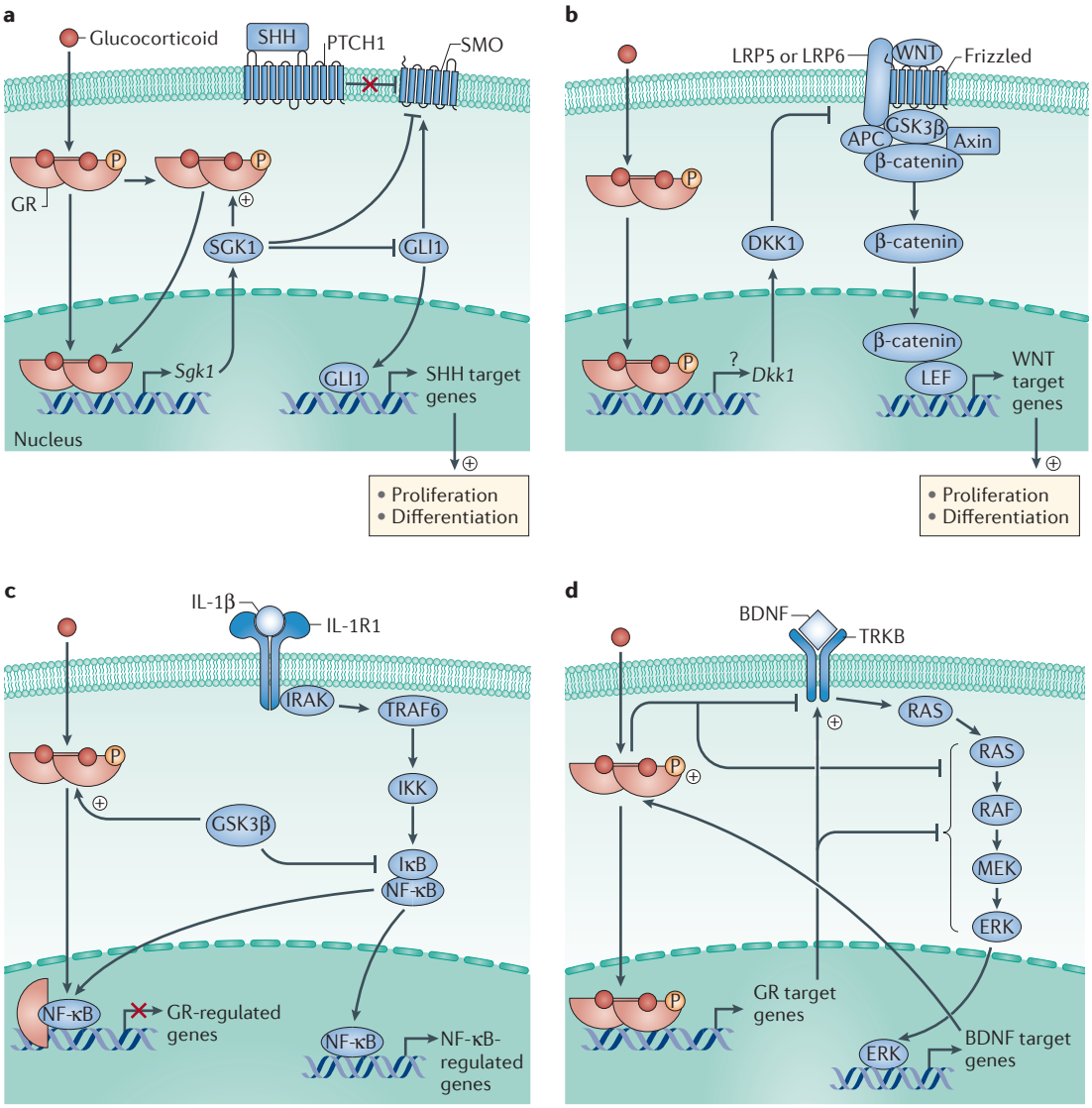
WNT proteins and their receptors are expressed in the neurogenic niche in the hippocampus, where, through canonical WNT signalling, they increase progenitor proliferation and differentiation[111]. Specifically, WNT3 is expressed by astrocytes in the hilus of the hippocampus and interacts with Frizzled receptors, which are mainly expressed in progenitor cells of the SGZ. There are several WNT signalling pathways, but the canonical WNT–β-catenin pathway seems to be involved in adult neurogenesis[111]. Interestingly, restraint stress in mice increases the hippocampal level of an inhibitor of the canonical WNT pathway, the protein Dickkopf 1 (DKK1)[112]. DKK1 is also involved in the decreased hippocampal volume induced by chronic stress[112]. In this study, a reduction in the expression of DKK1 prevented the stress-induced decreases in neurogenesis seen in control mice, indicating that the WNT pathway might be a link between these volume changes, stress and adult neurogenesis[112].

Crosstalk between pathways

The persistent discrepancies that have been found between studies of stress-related modulators of adult neurogenesis indicate that individual pathways and molecules do not function independently in the stress-induced regulation of adult neurogenesis. These discrepancies are, however, interesting, as they point to additional unknown mechanisms. As discussed below, recent evidence indicates that several of the described pathways interact and affect aspects of adult neurogenesis. This suggests that crosstalk between these modulators may be a mechanism that determines the outcome of stress on adult neurogenesis.

Morphogen signalling pathway crosstalk. As mentioned above, recent studies have shown that glucocorticoid stimulation and stress-induced activation of glucocorticoid receptors result in the expression of the kinase SGK1 in neurogenic human hippocampal cells and in animal models of stress[38,45]. SGK1 is known to inhibit another intrinsic pathway, the Hedgehog pathway, through down-regulation of SMO and the GLI transcription factor family (FIG. 4a). As a result, Hedgehog-mediated cell proliferation is disrupted, leading to its inhibition[45]. This indicates that the effect of stress on adult neurogenesis may involve an interaction between the glucocorticoid receptor signalling and Hedgehog pathways.

Morphogens
A group of signalling molecules that govern tissue development. They classically control morphogenesis through cell proliferation and differentiation.



Interestingly, in these same cells, high levels of glucocorticoids induced 'downstream' glucocorticoid receptor-dependent SGK1 upregulation, followed by SGK1-induced phosphorylation of 'upstream' cytoplasmic glucocorticoid receptors, resulting in their nuclear translocation. The net result of this effect was a decrease in cell proliferation[45]. Thus, SGK1 may decrease neurogenesis both directly, through Hedgehog inhibition, and indirectly, by potentiating upstream glucocorticoid receptor activity. Another interesting aspect of this interaction is that, once it is initiated, the effects of glucocorticoid receptor activation, including suppression of cell proliferation, continue even in the absence of glucocorticoids. These findings therefore suggest that, as mentioned above, in situations of high or chronic stress (that is, when glucocorticoid levels are high), glucocorticoid receptor transcriptional activity can potentially become independent of stimulation by glucocorticoids and thereafter be continued by other crosstalk pathways even after glucocorticoid levels have returned to normal.

In similarity to the study described above, a study in chronically stressed animals showed that glucocorticoid receptor transcriptional activity was independent of the levels of cytosolic or nuclear glucocorticoid receptor but rather was dependent on the cyclin-dependent-like kinase 5-mediated and JUN amino-terminal kinase (JNK)-mediated phosphorylation of a small number of nuclear glucocorticoid receptors[79]. Although the authors did not investigate the possible involvement of other pathways in the regulation of transcriptional activity of the glucocorticoid receptor, it is possible that these kinases exhibit crosstalk with, for example, IL-1β and tumour necrosis factor, which are known to activate JNK family proteins[113,114].

Another example of glucocorticoid crosstalk with morphogens is provided by a study in mice exposed to stress or corticosterone injections. Both manipulations result in increased DKK1 levels and, consequently, reduced WNT signalling in the hippocampus[112]. The stress-induced increase in DKK1 levels is attenuated in adrenalectomized mice and is dependent on

Figure 4 | **Potential crosstalk mechanisms relevant to stress and neurogenesis.** **a** | Activation of glucocorticoid receptors (GRs) leads to the expression of serum/glucocorticoid-regulated kinase 1 (SGK1). SGK1 can then increase phosphorylation of the GR, which increases GR translocation to the nucleus and subsequent gene expression, and leads to GR activation that is independent of glucocorticoids. SGK1 also initiates crosstalk with the Hedgehog signalling pathway by inhibiting both Smoothened (SMO) and GLI1, and this inhibits the Hedgehog pathway and ultimately decreases Hedgehog-mediated cell proliferation and cell differentiation. **b** | Data show that Dickkopf 1 (DKK1) levels are increased during stress through an unknown mechanism that is thought to be dependent on GRs. DKK1 is known to function as an inhibitor of the canonical wingless (WNT) pathway by preventing the binding of WNT to the low-density lipoprotein receptor-related protein 5 (LRP5) (or LRP6)–Frizzled receptor complex. Increased GR signalling may therefore lead to an induction of DKK1, which subsequently inhibits the WNT pathway. DKK1 may therefore act as a crosstalk mediator between GR signalling and the WNT pathway, ultimately leading to a decrease in cell proliferation and differentiation. **c** | Studies indicate that the decrease in neurogenesis seen during stress is dependent on both interleukin-1β (IL-1β) signalling and GR signalling, suggesting potential crosstalk between these two signalling pathways. The findings that nuclear factor-κB (NF-κB) is induced by IL-1β and, in addition, that NF-κB inhibits GR signalling and transcription of GR-regulated genes by interacting with GRs indicate that this may be a crosstalk mechanism to inhibit GR-mediated transcription. In addition, IL-1β signalling-mediated decreases in neurogenesis have been shown to involve glycogen synthase kinase 3β (GSK3β), as blocking GSK3β restores the negative effects of IL-1β. Moreover, GSK3β-mediated phosphorylation of GRs can inhibit interaction of the GR with its co-regulators, including NF-κB. Reduced GR–NF-κB interaction would lead to reduced NF-κB-mediated trans-repression of GR-regulated transcription. Thus, GSK3β signalling may be an additional crosstalk mechanism that occurs between IL-1β and GR signalling. **d** | Brain-derived neurotrophic factor (BDNF) has generally been shown to increase neurogenesis, although there are contradictory findings suggesting a greater complexity. The mechanisms through which stress alters BDNF expression and thus affects neurogenesis are also unclear. Studies indicate that crosstalk between GR signalling and BDNF signalling occurs, and this might add to the complexity of the interaction between stress and BDNF. In particular, glucocorticoid signalling inhibits aspects of the BDNF signalling pathway, including mitogen-activated protein kinase (MAPK) signalling, both through direct interaction with GRs as well as via GR target genes. Glucocorticoids acting through target genes can also paradoxically activate TRKB (tropomyosin-related kinase B) receptors and thus increase BDNF signalling. BDNF may also affect GR signalling by inducing phosphorylation of GRs. APC, adenomatous polyposis coli protein; ERK, extracellular signal-regulated kinase; IκB, inhibitor of NF-κB; IKK, IκB kinase; IL-1R1, IL-1 receptor type 1; IRAK, IL-1 receptor-associated kinase; LEF, lymphoid enhancer-binding factor; MEK, MAPK kinase; PTCH1, Patched 1; SHH, sonic hedgehog; TRAF6, TNF receptor-associated factor 6.

glucocorticoid receptors, as the glucocorticoid receptor antagonist mifepristone, but not the mineralocorticoid receptor antagonist spironolactone, inhibits this stress-induced increase. Transgenic mice in which DKK1 induction is defective also show increased neurogenesis in response to stress rather than the expected decrease seen in control mice[112]. These results indicate that the decrease in neurogenesis seen as result of stress is due in part to DKK1-mediated crosstalk between glucocorticoid receptor and WNT signalling (FIG. 4b).

Cytokine signalling pathway crosstalk. Several lines of evidence point to crosstalk between pro-inflammatory cytokines and glucocorticoid receptors in stress-induced regulation of adult neurogenesis. For example, one study showed that, in mice lacking IL-1R1, exposure to chronic stress does not increase plasma corticosterone levels or reduce hippocampal neurogenesis, suggesting that stress increases glucocorticoid signalling through an IL-1β-dependent mechanism. This is confirmed by the fact that chronic glucocorticoid administration reduces neurogenesis in these mice[91]. This finding suggests that the IL-1β-dependent mechanism that alters adult neurogenesis during chronic stress may be a crosstalk mechanism that also involves glucocorticoid receptors. However, *in vitro* treatment of cultured rat hippocampal progenitor cells with IL-1β decreases cell proliferation, and this is not affected by glucocorticoid receptor antagonists[69]. The fact that IL-1β decreases adult neurogenesis through glucocorticoid receptor signalling during chronic stress but apparently not *in vitro* suggests that the mechanism and signalling pathways involved may be different in different experimental settings.

The NF-κB and GSK3β signalling pathways are also involved in the IL-1β-dependent alterations of adult neurogenesis during chronic stress and may therefore be a part of the molecular mechanism that is involved in this IL-1β–glucocorticoid receptor crosstalk[93]. Numerous studies have found that glucocorticoid receptor signalling can inhibit NF-κB; however, it has also been shown that NF-κB can inhibit glucocorticoid receptor signalling through a CBP-mediated enhancement of the interaction between the NF-κB subunit p65 and the glucocorticoid receptor[115]. Thus, the crosstalk between NF-κB and the glucocorticoid receptor may be a mechanism through which IL-1β inhibits glucocorticoid receptor transcriptional activity (FIG. 4c). Although these studies were performed in a kidney cell line (COS-1)[115], this mechanism may theoretically also underlie IL-1β- and glucocorticoid receptor-induced inhibition of adult neurogenesis.

Phosphorylation may be one additional method by which crosstalk between the glucocorticoid receptor and other signalling pathways is enabled. GSK3β, for example, can not only alter protein–protein interactions but can also phosphorylate glucocorticoid receptors in human and other mammalian cell lines[78]. Moreover, in a HeLa cell line, GSK3β-mediated glucocorticoid receptor phosphorylation alters the ability of these receptors to recruit transcriptional co-regulators CBP and p300 and the NF-κB subunit p65, and thus modulates the glucocorticoid receptor-mediated expression profile by inhibiting NF-κB trans-repression[116]. This crosstalk between the GSK3β, NF-κB and glucocorticoid receptor pathways is interesting, because it provides a mechanism through which independent signalling pathways can converge with the classical stress-associated glucocorticoid receptor signalling pathway and potentially modulate the stress response by altering glucocorticoid receptor-mediated transcription. Although it remains to be seen whether GSK3β-mediated phosphorylation of glucocorticoid receptors is altered during stress and has effects on adult neurogenesis, the studies described in this section indicate that both of these outcomes are likely.

Neurotrophic factor signalling crosstalk. Glucocorticoids can inhibit BDNF expression in different tissues and cell types, as described in a recent review[117]. Furthermore, glucocorticoids can regulate BDNF signalling, including the level and activity of the mitogen-activated protein (MAP) kinase and phospholipase Cγ pathways downstream of BDNF[117]. Of relevance to adult neurogenesis, glucocorticoid receptor–BDNF crosstalk has been

described in hippocampus-derived neurons *in vitro*. Specifically, stimulation of developing hippocampal neurons through glucocorticoid receptors prevents BDNF-induced dendritic outgrowth and the expression of glutamate receptor subunits[118]. These glucocorticoid receptor-dependent effects are mediated by changes in the MAP kinase pathways (FIG. 4d). Furthermore, glucocorticoid receptor–BDNF crosstalk also leads to the inhibition of calcium influx in more mature neurons[118]. Glucocorticoid treatment of hippocampal cells also activates TRKB and promotes cell survival in neurons through a mechanism that is dependent on glucocorticoid receptor transcriptional activity[119]. Thus, these studies indicate that stress may negatively affect neurogenesis through the inhibitory crosstalk of glucocorticoid receptor signalling on BDNF signalling.

Conversely, it is possible that BDNF signalling modulates glucocorticoid receptor signalling and, through this mechanism, modulates adult neurogenesis. Indeed, such a mechanism may partly explain the discrepancy seen with exercise-induced increases in glucocorticoid levels, which paradoxically increase cell proliferation rather than decrease it. The theory that glucocorticoid receptors are modulated by BDNF is supported by the fact that the level of BDNF increases during exercise and could therefore potentially modulate the exercise-induced increases in glucocorticoid receptor signalling[120]. In a perhaps good example of crosstalk modulation, it was demonstrated in a recent study that, in cortical neurons, BDNF induces phosphorylation of specific glucocorticoid receptor residues, causing changes in glucocorticoid receptor-dependent gene transcription[121]. These studies support the idea that the crosstalk mechanism affecting glucocorticoid receptor transcriptional activity may be important in the BDNF-mediated regulation of adult neurogenesis.

Conclusions and perspectives

The neurobiology of stress involves many aspects, from the perception of our experiences as stressful to the brain changes that regulate our reactions. In this Review, we have depicted a complex picture in which glucocorticoid receptors are central to the effects of stress on adult neurogenesis, but the glucocorticoid receptor-mediated effects on the different stages of neurogenesis may depend on numerous mechanisms through which glucocorticoid receptor activity can be modulated. A potentially important instigator of this modulation may be crosstalk with other signalling pathways. If indeed these types of crosstalk are common, then it may be beneficial to take this into consideration when planning and interpreting experiments to understand stress.

Moreover, crosstalk mechanisms could potentially have clinical implications, specifically for stress-related pathologies such as depression and anxiety disorders. The role of impaired adult neurogenesis in these disorders has been the focus of many studies, and it has been extensively reviewed elsewhere[16,122]. In brief, studies using animal models have identified adult neurogenesis as being an important aspect of the mechanism through which commonly used antidepressants achieve their therapeutic action[18,123]. In addition, decreased adult neurogenesis is seen in rodent models of depression. However, it is important to emphasize that direct evidence from post-mortem human studies with regards to depression is still unclear, although one study has reported an increase in neurogenesis by antidepressants[124]. Whether adult neurogenesis is causal in the precipitation of depression is still a matter of debate[16]; depression is a complex multifactorial disorder that probably results from numerous pathological mechanisms, which range from disruption of noradrenergic and serotonergic pathways in the brain to increased inflammation in the blood and which are underpinned by both genetics and environmental risk factors. Potential crosstalk between the signalling pathways described in this Review may be one means through which these different pathological mechanisms converge to affect adult neurogenesis and eventually precipitate depression. If indeed a decrease in adult neurogenesis is important in the development of these pathologies, then future studies may target mediators of the signalling pathways involved in this crosstalk, in order to fully understand and efficiently treat these diseases and to identify novel targets for future treatment strategies.

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Acknowledgements
C.M.P. and P.A.Z. are supported by the National Institute of Health Research Biomedical Research Centre in Mental Health at South London and Maudsley NHS Foundation Trust and King's College London, and by the Medical Research Council UK (MR/J002739/1 and MR/L014815/1). M.E. is supported by a Marie Curie Fellowship from the European Commission and a grant from the Lundbeck Foundation. The authors thank S. Thuret and T. Murphy for discussions on this Review.

Competing interests statement
The authors declare competing interests: see Web version for details.