Stress signalling pathways that impair prefrontal cortex structure and function

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Abstract

The prefrontal cortex (PFC)—the most evolved brain region—subserves our highest-order cognitive abilities. However, it is also the brain region that is most sensitive to the detrimental effects of stress exposure. Even quite mild acute uncontrollable stress can cause a rapid and dramatic loss of prefrontal cognitive abilities, and more prolonged stress exposure causes architectural changes in prefrontal dendrites. Recent research has begun to reveal the intracellular signalling pathways that mediate the effects of stress on the PFC. This research has provided clues as to why genetic or environmental insults that disinhibit stress signalling pathways can lead to symptoms of profound prefrontal cortical dysfunction in mental illness.

The prefrontal cortex (PFC) intelligently regulates our thoughts, actions and emotions through extensive connections with other brain regions (BOX 1). It creates a "mental sketch pad" (to use a phrase coined by Alan Baddeley) through networks of neurons that can maintain information in the absence of environmental stimulation[1]. Neuroscientists such as Patricia Goldman-Rakic referred to this process as working memory: the ability to keep in mind an event that has just occurred, or bring to mind information from long-term storage, and use this representational knowledge to regulate behaviour, thought and emotion[2]. The PFC is able to protect these fragile representations from the interference of external or internal distractions, and is key for inhibiting inappropriate actions and promoting task-relevant operations (so-called 'top-down' regulation)[3–6]. PFC operations allow the flexible regulation of behaviour to enable us to properly respond to a changing environment — for example, the ability to shift attentional set to new dimensions and to alter decision making as reward contingencies shift[7,8]. The PFC also monitors errors, giving us the insight that we are incorrect and need to shift strategies[9]. All of these abilities depend on proper PFC neuronal network connections, which are highly sensitive to their neurochemical environment.

This Review discusses how neuromodulatory changes that occur during stress rapidly disrupt PFC network connections and markedly impair PFC function. It focuses on the spatial working memory functions of the PFC because the circuitry, physiology and

modulation of the dorsolateral PFC neurons that mediate working memory are the best characterized of this brain region. The Review first describes how exposure to even mild uncontrollable stress can rapidly impair PFC functions in humans and animals. It then describes the extracellular and intracellular mechanisms that contribute to PFC deficits, and how chronic stress exposure leads to structural changes in the PFC. Finally, it highlights how genetic and environmental changes in stress signalling pathways are associated with mental illness, and how an understanding of these pathways might lead to better treatments for neuropsychiatric disorders.

Acute stress impairs PFC function

Human studies

Some of the first studies on the effects of stress on cognition began after the Second World War, based on observations that pilots who were highly skilled during peacetime often crashed their planes in the stress of battle owing to mental errors[10]. Research was initiated to experimentally manipulate stress levels to see how this altered performance and cognitive abilities[11]. Many of these early studies showed that stress exposure impaired the performance of tasks that required complex, flexible thinking, but that it could actually improve the performance of simpler and/or well-rehearsed tasks[10,12]. We now understand that the types of tasks that were impaired by stress were those that required PFC operations[13], whereas engrained habits that rely on basal ganglia circuits were spared or enhanced[14].

These early studies also pointed to the essential role of the subject's sense of control over the stressor. Subjects who felt in control of the situation (even if this was an illusion) were often not impaired by stress exposure, whereas those who felt out of control were impaired15. Animal studies have confirmed the key role of control16. The control factor poses a particular problem for modern stress research in human subjects, as ethically all subjects must be given control of their situation and be able to leave the experiment at any time. Nonetheless, paradigms have emerged that are effective in creating a sense of uncontrollable stress in an experimental setting. For example, one functional imaging study had female subjects watch emotionally upsetting movies and found evidence of reduced activation in PFC regions17. emotional distractors can similarly diminish dorsolateral PFC activity in subjects performing a working memory task18. Many studies of hormonal responses to stress have used a public speaking task as an effective stressor (the Trier social stress test). This social stressor has been found to impair cognitive flexibility19 and working memory20, both of which require PFC function. Interestingly, this same social stressor actually improved classical conditioning for negative stimuli, as well as hippocampal spatial memory20. These findings in humans are highly consistent with animal studies showing that acute mild stress impairs prefrontal function but actually improves the functioning of the amygdala and hippocampus (see below). other studies have found impaired PFC function in subjects using mental imagery of their own overwhelming experiences21,22 and in medical students as they studied for the Boards23.

The reduction in PFC functioning that occurs during stress is highly relevant to understanding human mental and physical health. loss of self-control during stress exposure can lead to relapse of a number of maladaptive behaviours, such as drug addiction, smoking, drinking alcohol and overeating22. Prolonged stress is a major risk factor for depression24,25, and exposure to traumatic stress can cause post-traumatic stress disorder (PTSD)26. Stress can also exacerbate the symptoms of schizophrenia27,28 and bipolar disorder by, for example, switching patients from a period of normalcy (euthymia) into a manic state29. Given these powerful effects on human health, it is important to have animal

models of the stress response to help us understand the mechanisms that render us vulnerable.

Animal studies

Early studies of the effects of stress on performance in rodents used the so-called learned helplessness paradigm. These studies were among the first to show that uncontrollable stress (that is, inescapable shock) but not controllable stress impaired performance on a Y-maze task owing to deficits in selective attention[16]. More recent studies using this paradigm have shown that when the animal perceives itself as being in control the PFC is key for suppressing stress responses triggered in the brainstem30. Indeed, the PFC and the hippocampus are the two brain structures that are positioned to inhibit the glucocorticoid stress response31.

Several studies have used tasks that explicitly rely on PFC function to examine the effects of mild stress on cognitive performance. These studies used spatial working memory tasks in rats and monkeys and found that quite mild acute stress impaired the accuracy of responding and often produced a perseverative pattern of response that is consistent with PFC dysfunction[32–34]. For example, a white-noise stress that impairs cognitive abilities in humans was found to also impair spatial working memory in monkeys[33]. Conversely, performance of control tasks with similar motor and motivational demands but no need for PFC regulation was not altered by mild stress exposure. Similarly, rats exposed to acute stressors were impaired on a spatial delayed alternation task that requires medial PFC function, but were not impaired on a non-PFC-reliant spatial discrimination task in the same maze[32].

By contrast, acute mild stress exposure has no effect on or can actually improve the memory consolidation functions of the hippocampus and the amygdala35,36. (Note that the ventromedial PFC regulates the fear responses mediated by the amygdala; see REF. [37] for a recent review.) More severe acute stressors impair hippocampal functions38 but continue to strengthen the emotional associations and motor habits carried out by the amygdala and striatum, respectively14,39. Thus, acute uncontrollable stress impairs PFC-mediated cognitive functions in humans and animals and switches the control of behaviour and emotion to more primitive brain circuits.

Box 1| Prefrontal cortical versus amygdala circuits: the switch from non-stress to stress conditions

The prefrontal cortex (PFC) has extensive connections with other cortical and subcortical regions that are organized in a topographical manner, such that regions that regulate emotion are situated ventrally and medially (green area in part **a** of the figure) and regions that regulate thought and action are situated more dorsally and laterally (blue and blue–green areas in part **a**). The dorsolateral PFC (DLPFC) has extensive connections with sensory and motor cortices and is key for regulating attention, thought and action163. In humans, the right inferior PFC (rIPFC) seems to be specialized for inhibiting inappropriate motor responses4. By contrast, the ventromedial PFC (VMPFC) has extensive connections with subcortical structures (such as the amygdala, the nucleus accumbens and the hypothalamus) that generate emotional responses and habits164−166 and is thus able to regulate emotional responses. Finally, the dorsomedial PFC (DMPFC) has been associated with error monitoring9 and, in human functional MRI studies, reality testing167. These PFC regions extensively interconnect to regulate higher-order decision making and to plan and organize for the future. Under non-stress conditions (see part **a** of the figure), the extensive connections of the PFC orchestrate the brain's activity for

intelligent regulation of behaviour, thought and emotion. The PFC also has direct and indirect connections to monoamine cell bodies in the brainstem, such as the locus coeruleus (LC) (where noradrenaline projections arise) and the substantia nigra (SN) and ventral tegmental area (VTA) (where the major dopamine projections originate), and thus can regulate its own catecholamine inputs. Optimal levels of catecholamine release in turn enhance PFC regulation, thus creating a 'delicious cycle'. Under conditions of psychological stress (see part **b** of the figure) the amygdala activates stress pathways in the hypothalamus and brainstem, which evokes high levels of noradrenaline (NA) and dopamine (DA) release. This impairs PFC regulation but strengthens amygdala function, thus setting up a 'vicious cycle'. For example, high levels of catecholamines, such as occur during stress, strengthen fear conditioning mediated by the amygdala[168]. By contrast, stress impairs higher-order PFC abilities such as working memory and attention regulation. Thus, attention regulation switches from thoughtful 'top-down' control by the PFC that is based on what is most relevant to the task at hand to 'bottom-up' control by the sensory cortices, whereby the salience of the stimulus (for example, whether it is brightly coloured, loud or moving) captures our attention5. The amygdala also biases us towards habitual motor responding rather than flexible, spatial navigation14. Thus, during stress, orchestration of the brain's response patterns switches from slow, thoughtful PFC regulation to the reflexive and rapid emotional responses of the amygdala and related subcortical structures.

Catecholamines mediate acute-stress effects

How do neurochemical changes evoked by exposure to acute stress impair PFC function? PFC working memory abilities crucially depend on the precise activity of interconnected neuronal networks. The microcircuitry that subserves spatial working memory in primates has been an attractive model for study, as the anatomy, physiology and neuromodulation of these networks are well characterized owing to the pioneering work of Goldman-Rakic and colleagues[40]. This Review focuses on catecholamine modulation of spatial working memory circuits, as this is currently the arena where we best understand how stress-like alterations in the chemical environment alter neuronal response patterns in primate prefrontal networks that are actively engaged in a cognitive operation. It is hoped that future studies will extend this approach to other cortical regions, additional cognitive operations and other key neuromodulators.

The circuits that underlie spatial working memory have been mapped in great detail. In the primate cortex, highly processed visual spatial information is fed forward from the parietal association cortices to the principal sulcal cortex in the dorsolateral PFC[40]. This area is crucial to spatial working memory, as lesions in this area but not in the surrounding tissue produce profound and permanent deficits on spatial working memory tasks[40]. Microcircuits in the PFC can maintain representations of visuospatial information in the absence of environmental stimulation — for example, during the delay period in a working memory task. Funahashi *et al.*[41] developed a task to probe the spatial working memory circuitry, called the oculomotor delayed response (ODR) task (FIG. 1). In this task, the monkey has to remember a precise spatial location over a delay period before moving its eyes to the remembered location to receive a juice reward (FIG. 1a). each session consists of hundreds of trials, with the correct spatial position changing between trials. Thus, the contents of working memory must be constantly updated. Single units are recorded from the PFC (FIG. 1b) while the monkey performs the ODR task. In this region many neurons show highly tuned, persistent activity during the delay period; this activity represents spatial position in the absence of environmental stimulation (for example, see FIG. 1c). The persistence of neuronal activity during the delay period is thought to arise from recurrent excitation between PFC pyramidal cells with shared inputs from the parietal cortex — that is, between

pyramidal cells with similar spatial characteristics (FIG. 1d). These excitatory recurrent connections probably involve NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor synapses onto dendritic spines. By contrast, the high degree of spatial tuning arises from the activity of local inhibitory interneurons (for example, GABA (γ-aminobutyric acid)-ergic basket cells and chandelier cells (FIG. 1d)), which provide lateral inhibition. Thus, when pyramidal cells representing, for example, spatial positions ~90° from a central reference point are active, they excite each other to create persistent activity and at the same time activate GABAergic interneurons that suppress the activity of pyramidal cells representing other directions (such as the cells dedicated to 45°). In this example, 90° would be called the 'preferred direction' of the excited neurons and other spatial positions would be referred to as the 'non-preferred directions' for those neurons. Although glutamate and GABA are the foundation of this spatially tuned, mnemonic firing, the strength of the persistent firing and the degree of spatial tuning are also powerfully influenced by the catecholamines noradrenaline and dopamine.

Noradrenaline and dopamine neurons in the brainstem change their firing rate according to our arousal state and according to the relevance of events in the environment. Noradrenaline neurons in the locus coeruleus are silent during rapid eye movement sleep and have low tonic firing during slow wave sleep, moderate tonic firing and pronounced phasic firing to relevant stimuli during non-stressed waking, and high tonic firing with dysregulated phasic firing during stress[42]. They fire to relevant stimuli during alert waking but can fire to irrelevant stimuli (distractors) during fatigue or stress[42]. Dopamine neurons have not been followed as methodically with regard to states of arousal, but in general increased phasic firing is related to prediction of reward43. However, recent studies suggest that a subset of midbrain dopamine neurons increase their firing to aversive stimuli44, and it is possible that these underlie the changes in PFC function that occur during stress. Importantly, both dopamine and noradrenaline release are increased in the PFC during exposure to acute stress45,46. Indeed, even very mild stress increases dopamine release in the PFC[47].

Although the noradrenaline and dopamine innervation of the PFC is quite delicate[48], it is extraordinarily powerful. Noradrenaline and dopamine each have an 'inverted U'-shaped influence on working memory whereby either too little or too much noradrenaline and/or dopamine impairs PFC function (FIG. 2). Noradrenaline and dopamine each provide essential excitatory influences that put the cortex into an awake state in which neurons can process and exchange information[49,50]. However, they also have additional modulatory influences that powerfully influence the strength of PFC connections as networks engage in working memory operations.

The inverted U-shaped relationship between noradrenaline levels and working memory is especially interesting, as noradrenaline engages different types of receptors with varying levels of release. Noradrenaline has highest affinity for α_2-adrenergic receptors, and lower affinity for α_1- and β-adrenergic receptors[51]. As shown in FIG. 2, the levels of noradrenaline that are released during alert, non-stressed waking optimize working memory by engaging α_{2A}-receptors[52,53], whereas the high levels of noradrenaline that are released during stress impair PFC function by stimulating lower-affinity α_1-receptors[54] and β_1-receptors[55]. Thus, either depletion of noradrenaline[52] or blockade of α_{2A}-receptors in the PFC[53] impairs working memory, whereas stimulation of postsynaptic α_{2A}-receptors in the PFC improves working memory performance[52,56–58]. These effects can be seen at the cellular level too: inadequate α_{2A}-receptor stimulation reduces PFC firing, whereas α_{2A}-receptor stimulation in the PFC enhances neuronal firing during the delay period for the neurons' preferred direction in the ODR task[59,60] (FIG. 2a). By contrast, high levels of α_1-receptor stimulation in the PFC rapidly suppress neuronal firing and impair spatial working memory

performance[61,62]. Similarly, stress-induced cognitive deficits can be prevented by administration of α_1-receptor antagonists in the PFC or systemically[54]. These findings are consistent with clinical investigations showing that the α_1-receptor antagonist prazosin is useful in treating PTSD[63,64]. Studies in humans have also found that a β-receptor antagonist can prevent stress-induced impairment of cognitive flexibility[19]. Thus, there is good agreement between the animal and human studies.

Dopamine exerts its inverted U-shaped influence on working memory abilities through actions at the D1 receptor family (as current drugs cannot dissociate D1 and D5 receptors, their respective contributions are not understood). Both blockade and excessive stimulation of D1 receptors impair spatial working memory[65–67]. Working memory deficits during stress exposure involve excessive D1 receptor stimulation, as they are prevented by D1 antagonist administration32. The inverted U-shaped relationship can also be observed at the cellular level (FIG. 2b), where an optimal level of D1 receptor stimulation enhances spatial tuning by suppressing delay-related firing to the neurons' non-preferred directions in the ODR task[68]. Thus, dopamine and noradrenaline have complementary roles: α_{2A}-receptor stimulation enhances network firing for shared inputs (that is, it increases the 'signal' (REF. 60)), whereas D1 receptor stimulation sculpts neuronal firing by decreasing firing to non-preferred inputs (that is, it decreases 'noise' (REF. 68)). However, at higher levels of D1 receptor stimulation, firing is suppressed for all directions and the neuron loses both its spatial tuning and its level of responsiveness68 (FIG. 2b). Thus, high levels of catecholamines during stress reduce both the persistent firing and the tuning of PFC neurons. It is likely that the D2 family of dopamine receptors contributes to the stress response as well. excessive D2 receptor stimulation impairs PFC working memory function in animals[69] and humans[70] and is associated with increased response-related firing in monkeys[71] and increased response-related blood oxygen level-dependent signals in human imaging studies[70]. The inverted u-shaped relationship between dopamine levels and PFC functioning has been observed in humans both in pharmacological studies[72] and with regard to catechol-*O*-methyltransferase (COMT) genotype[73]: the methionine substitution in the COMT protein that results from one of the *COMT* polymorphisms reduces the ability of COMT to catabolize dopamine and increases vulnerability to stress- or stimulant-induced working memory impairments in human subjects[74] and in mice[75].

It is noteworthy that stress-induced impairments in working memory can be rescued by blocking either D1 or α_1-receptors in the PFC. These findings are consistent with synergistic interactions between dopamine and noradrenaline effects. The catecholamine actions might also synergize with glucocorticoid effects in the PFC. Stress increases the release of glucocorticoids as well as that of catecholamines, and studies in both animals[76] and humans[77] have shown that high levels of glucocorticoids by themselves can impair working memory. These effects of glucocorticoids are rapid and presumably do not occur through traditional genomic mechanisms. It is possible that glucocorticoids exaggerate catecholamine actions in the PFC by blocking the extraneuronal catecholamine transporters on glia that clear the extrasynaptic space of catecholamines[78]. Such a synergistic relationship between glucocorticoids and cat-echolamines has already been observed in the amyg dala, where glucocorticoids and α_1- and β-receptor actions reinforce memory consolidation[79,80].

The amygdala plays a key part in changing the neurochemical environment of the PFC during stress. lesions to the amygdala prevent the increase in dopamine and noradrenaline release that occurs in the PFC in response to a psychological stressor[81]. As shown in BOX 1, under stress conditions the amygdala projections to the brain-stem and to the hypothalamus stimulate the release of catecholamines and glucocorticoids throughout the neuraxis. These high levels of catecholamines and glucocorticoids strengthen amygdala functions, such as

fear conditioning and consolidation of emotionally relevant information[79,80], but weaken PFC functioning; thus they shift the orchestration of brain responses from the PFC to the amygdala. High levels of catecholamines also strengthen the functioning of other subcortical brain regions and posterior cortical areas. For example, high levels of noradrenaline acting at α_1- and β-receptors enhance memory consolidation processes in the hippo-campus[82,83] and increase the signal/noise ratio in primary sensory cortices[84−86]. Higher levels of dopamine release also promote habit formation in the basal ganglia[87]. It is possible that high levels of dopamine release in corticobasal ganglia circuits during stress serve to capture whatever successful behaviour has just rescued subjects from danger and engrain this pattern as a habit. But this same evolutionary solution could make humans vulnerable to maladaptive behaviours (for example, motor tics, drug addiction and auditory hallucinations) when an inappropriate behavioural pattern is 'captured' by high dopamine levels. Taken together, the evidence indicates that high levels of catecholamine release initiated by the amyg dala during stress switch the brain from thoughtful, reflective regulation by the PFC to more rapid reflexive regulation by the amygdala and other subcortical structures (BOX 1). These mechanisms might save our life when we are in danger and need to react rapidly, but they can be detrimental when we need to make choices that require thoughtful analysis and inhibitory control.

Intracellular signalling pathways

The intracellular mechanisms that cause the loss of PFC working memory function during acute stress are now beginning to be understood, and they provide important clues for understanding the genetic basis and treatment of mental illness. A summary of these signalling pathways and their interactions can be seen in FIG. 3.

High levels of α_1-adrenergic receptor stimulation during stress impair PFC working memory function by activating phosphatidylinositol–protein kinase C (PKC) intracellular signalling pathways. In rodents the working memory deficits that are caused by pharmacological stress, cold water stress or administration of α_1-agonists can be reversed by infusing PKC inhibitors directly into the PFC[61,88]. Conversely, stress-induced working memory impairments can be mimicked by infusing a PKC activator into the PFC[61]. Similar effects are observed at the cellular level: the suppression of PFC neuron firing that is induced by α_1-receptor stimulation can be reversed by iontophoresis of a PKC inhibitor[61]. *In vitro* recordings from PFC slices have shown that the inositol-1,4,5-tris-phosphate (InsP$_3$)-Ca^{2+} arm of phosphatidylinositol signalling is also important[89]. As shown in FIG. 4g, activation of phosphatidylinositol signalling liberates InsP$_3$, which can release Ca^{2+} from intracellular stores in dendrites. With adequate InsP$_3$ generation, waves of Ca^{2+} release are triggered, which can travel towards the soma and suppress neuronal firing by opening small-conductance, Ca^{2+}-activated/K$^+$ channels (SK channels) on the soma, leading to a current (I_{SK})[89]. In addition, Ca^{2+} liberation facilitates PKC activity by causing it to translocate from the cytosol to the membrane, where it is activated by diacylglycerol (DAG) (FIG. 3). Intracellular Ca^{2+} release also activates a depolarizing current, I_{CAN}, which restores neuronal firing[89] (FIG. 3). However, I_{CAN} is suppressed by high levels of PKC and cyclic AMP activity, and thus might not restore normal firing under conditions of stress, when PKC and cAMP activity are high.

High levels of catecholamines during stress can also impair PFC functioning through excessive cAMP signalling. The cAMP intracellular signalling cascade has power ful effects on working memory network activity and cognitive function. cAMP frequently acts through protein kinase A (PKA) signalling, and it is likely that many plastic processes in the PFC require PKA signalling, just as plastic processes in other brain regions do[90]. For example, memory consolidation over long delays (~30 min or more) requires prefrontal–hippocampal

interactions that benefit from cAMP activation of PKA. However, cAMP can also act at two other targets, namely exchange protein activated by cAMP (EPAC; also known as RAPGEF3)[91] and hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN channels)[92]. Physiological data indicate that cAMP might have particularly powerful effects on working memory networks through actions on HCN channels. cAMP increases the probability that HCN channels will open93 and allow passage of both Na^+ and K^+ (this is also referred to as the h current or I_h). HCN channels are localized on both the dendritic shafts and the dendritic spines of PFC pyramidal cells[60] (FIG. 4). HCN channels on dendritic shafts probably have the traditional role of helping to depolarize the neuron when the cell has become hyperpolarized. Indeed, extensive blockade of HCN channels with high doses of ZD7288 induces a loss of cell firing, consistent with loss of this depolarizing influence[60]. However, HCN channels on spines seem to have a more exquisite role, gating network inputs onto spines. HCN channels are localized next to α_{2A}-adrenergic receptors[60] or dopamine D1 receptors (C. Paspalas and A.F.T.A., unpublished observations) on spines near asymmetric (presumably excitatory) synapses. Thus, the catecholamine receptors can regulate cAMP levels in a confined cellular compartment, and so determine the state of HCN channels (open or closed) near synaptic inputs on the spine (FIG. 4a). When HCN channels are opened in the presence of cAMP they shunt nearby inputs. Recent data suggest that this shunting arises from opening of K^+ channels (Kv7 channels), giving rise to a hyperpolarizing M current[94]. High levels of cAMP might potentiate these actions through PKA modulation of Kv7 channels95, thus producing a coordinated cAMP shunting of network inputs.

Under optimal arousal conditions (alert but not stressed), HCN and Kv7 channel opening would be tightly regulated. Physiological and behavioural data indicate that under such conditions α_{2A}-receptor stimulation strengthens network inputs from neurons with shared spatial characteristics by inhibiting cAMP–HCN (and possibly cAMP–PKA–Kv7) signalling[60]. For example, blocking HCN channels with low doses of ZD7288 reverses the effects of α_{2A}-receptor blockade and restores normal network activity[60]. Similarly, infusion of low doses of ZD7288 or knockdown of HCN1 channels in the rat PFC improves working memory performance[60]. Conversely, we propose that in an ODR task, D1 receptors suppress neuronal responses to non-preferred directions by increasing cAMP production[68] and opening HCN channels on spines that receive network inputs from cells that are tuned to these other directions (FIG. 4a). Thus, under optimal conditions cAMP production would be tightly controlled and confined to a specific subset of spines receiving input from neurons that are irrelevant to current task demands. under these conditions, HCN channels on dendrites would be closed and PFC cell firing would be highly patterned (FIG. 4d).

By contrast, under conditions of uncontrollable stress there is excessive production of cAMP and impairment in working memory. The impairment in working memory that is induced by stress exposure or excessive D1 receptor stimulation can be prevented by blocking cAMP activity or HCN channels in the PFC60,[68] (A.F.T.A., unpublished observations) or can be mimicked by administering the cAMP analogue Sp-cAMPS[96]. Similar results are observed at the cellular level, whereby Sp-cAMPS, high doses of D1 agonist or a phosphodiesterase inhibitor all suppress neuronal firing in monkeys performing a working memory task, whereas inhibition of cAMP or gentle blockade of HCN channels restores normal firing patterns60,[68]. These findings are schematically illustrated in FIG. 4e,f, which show that high levels of cAMP during stress open HCN channels throughout the dendrite, weakening network inputs from all directions (FIG. 4e). loss of excitatory network inputs on spines would hyperpolarize the cell, which could open HCN channels on dendritic shafts to help to maintain some cell firing (FIG. 4f). under these conditions, the cell would show greatly reduced and unpatterned activity, as schematically diagrammed in FIGS 2,4h.

Stress signalling pathways have several feedforward interactions that could further contribute to the rapid and dramatic changes in brain responses to an acute stressor (FIG. 3). For example, cAMP–PKA signalling can stimulate the phosphorylation of InsP$_3$ receptors, which promotes InsP$_3$-mediated Ca^{2+} release[97]. Conversely, intracellular Ca^{2+} release from increased phosphatidylinositol signalling can activate Ca^{2+}-sensitive adenyl cyclases to increase cAMP signalling[98] (FIG. 3). Both cAMP[99] and PKC[100] signalling reduce the depolarizing current I$_{CAN}$, which would further weaken persistent firing[89,101,102]. Glucocorticoid release during stress could further potentiate these pathways through non-genomic activation of PKC signalling[103] (although it is not specifically known whether glucocorticoids have this effect in the PFC). These synergistic interactions would be needed to rapidly switch the control of behaviour from the PFC to more reflexive subcortical pathways in the presence of acute danger.

Chronic-stress effects on the PFC

Compared with exposure to acute stress, exposure to chronic stress leads to more extensive alterations in the rat prelimbic PFC, including architectural changes. The layer II/III neurons that form PFC networks lose dendritic material — that is, dendrite length, branching and spine density are reduced by chronic stress[104,105]. Spine loss is particularly evident at distal sites (~200 μm from the soma), and the mushroom-shaped spines that are probably involved in established synaptic connections seem to be particularly vulnerable[106]. These dendritic changes in the rat PFC are associated with marked PFC dysfunction in attentional set shifting[107] and working memory (A.B. Hains and A.F.T.A., unpublished observations). Chronic stress also disrupts the plastic relationship between the PFC and the hippocampus that is needed for flexible memory consolidation[108]. The dendritic changes in the PFC gradually reverse when the stress abates[109].

As with acute stress, the PFC seems to be particularly sensitive to architectural changes induced by chronic stress compared with other brain regions. Whereas structural changes in the hippocampus require several weeks of stress exposure[35], dendrites in the PFC begin to change after only one week of stress[110] or possibly even a single exposure[111]. By contrast to the PFC and hippocampus, dendrites in the amygdala expand in response to chronic stress exposure[112]. Thus, chronic stress weakens the structures that provide negative feedback on the stress response and strengthens the structures that promote the stress response. Interestingly, recent data indicate that neurons in the rat infralimbic PFC that project to the amygdala do not lose their dendrites in response to stress, highlighting the distinct response of amygdala circuits[113].

The signalling mechanisms that underlie dendritic changes in the PFC are just beginning to be studied. Chronic stress alters catecholamine pathways, increasing noradrenergic innervation of the PFC[114] (although dopamine becomes depleted with severe chronic stress[115]). Increased noradrenaline might lead to higher levels of PKC and cAMP signalling. We have found that increased PKC signalling contributes to spine loss, as daily treatment with a PKC inhibitor protects PFC spine density and working memory from the detrimental effects of chronic stress (A.B. Hains and A.F.T.A., unpublished observations). Stress-induced changes in dendritic morphology can be mimicked by chronic administration of high doses of glucocorticoids[116,117], which may involve excitotoxicity or oxidative stress[118]. Chronic glucocorticoid exposure also reduces brain-derived neurotrophic factor levels in the PFC[119], as does chronic stress[120], but it is not yet known whether this contributes to the observed dendritic changes.

Chronic stress during brain development or in childhood may have a particularly large effect on PFC structure and function in adulthood. Dendritic changes can occur *in utero* when the

mother is exposed to stress[121]. Chronic, uncontrollable stress in childhood might also have enduring effects on the adult PFC. For example, rat pups exposed to extensive maternal deprivation have enduring dendritic retraction in the PFC and increased anxiety-like behaviours[122]. By contrast, exposure to a mild stress, for example when a juvenile monkey learns that the mother will return after a short period of separation, seems to encourage resilient responses to stress in adulthood[123] and reduces glucocorticoid receptor expression in the dorsolateral PFC[124]. Similar effects have been shown to occur in rats, in which very mild stress early in life promotes resilience whereas more severe stressors exacerbate the stress response later in life[125]. Changes *in utero* and during childhood probably contribute to the susceptibility to formal mental illnesses that emerge during adolescence and adulthood[126].

Genetic and environmental factors

Both genetic and environmental factors can dysregulate stress signalling pathways in the PFC. They can weaken PFC abilities and, in some cases, lead to symptoms of mental illness.

Genetic insults

Some genetic variations in genes that encode enzymes which catabolize catecholamines that lead to relatively subtle effects on PFC function. For example, methionine substitutions in COMT increase the stress response in mice[75] and make humans more susceptible to cognitive impairment following stress and psychostimulant medication[74]. Similarly, a genetic variation in the promoter region for the monoamine oxidase A gene (MAOA) increases antisocial behaviours in boys exposed to the stress of child abuse[127].

Alterations in genes that encode molecules which serve as the intracellular brakes on the stress signalling pathways are associated with serious mental illness (FIG. 3). For example, disrupted in schizophrenia 1 (DISC1) normally provides negative feedback on cAMP signalling, but a mutation in *DISC1* decreased the activity of the phosphodiesterase PDE4B in the presence of high concentrations of cAMP[128]. loss-of-function translocations in *DISC1* are associated with high rates of mental illness[129], and with reduced PFC grey matter and impaired working memory in patients with schizophrenia[130]. DISC1 is important for the development of the PFC[131], but it is also likely that loss of function of DISC1 leads to increased cAMP–HCN signalling in spines[132] and thus to PFC network disconnection. Another important molecular brake on stress signalling pathways is regulator of G-protein signalling 4 (RGS4), which inhibits G_q signalling. RGS4 is normally concentrated in the dendritic stem, where Ca^{2+} waves that shut off PFC cell firing are generated[133]. RGS4 levels are greatly reduced in the PFC of patients with schizophrenia[134,135], and there is evidence of genetic alterations in *RGS4* in some families with schizophrenia or bipolar disorder[136,137]. loss of RGS4 function would disinhibit phosphatidylinositol–PKC signalling, leading to reduced PFC neuronal firing and susceptibility to spine loss. Finally, DAG kinase-η (DGKH) has been identified as the gene that is most strongly associated with bipolar disorder[138]. DGK is the enzyme that hydrolyses DAG and stops the activation of PKC. Importantly, medications for these disorders indirectly inhibit the PKC signalling pathway (for example, lithium suppresses phosphatidylinositol signalling), and the atypical antipsychotic medications block α_1-adrenergic and serotonin (5-hydroxytryptamine, 5-HT) type 2 (5-HT$_2$) receptors, which are coupled to G_q signalling[139,140]. There is recent evidence that lithium can restore PFC activity and grey matter levels in patients with bipolar disorder[141–143]. Thus, medications that correct the consequences of genetic insults could restore normal structure and function.

Environmental insults

Stressors sometimes take the form of environmental insults that threaten our safety. exposure to traumatic stressors can exaggerate subsequent stress responses and lead to PTSD. PTSD is associated with reduced medial PFC activity and grey matter volume[144] and with heightened noradrenaline activity145. Imaging studies have shown that experiencing trauma-related distractor stimuli disrupts working memory networks in patients with PTSD146. Similar effects have been seen in patients with depression147. Interestingly, post-pubertal, pre-menopausal women are at much higher risk for PTSD and depression[148], and intact female rats (that is, rats with normal oestrogen levels) are more sensitive to stress-induced PFC dysfunction than are male rats or ovariectomized females[34,149]. This suggests that oestrogen might amplify the PFC response to environmental insults.

Various toxins can impair PFC function by exaggerating the activity of stress signalling pathways. For example, drugs of abuse such as cocaine produce excessive dopamine signalling in the PFC, which weakens PFC function[150], including the ability to resist taking drugs. This triggers a vicious cycle because the subsequent drug taking leads to increasingly weaker PFC regulation of behaviour. Drug taking is especially prevalent during stress, when PFC function is further weakened by stress signalling pathways[22].

Another important environmental toxin is lead. lead is a divalent cation that mimics Ca^{2+} and potently activates PKC signalling[151]. Administration of low levels of lead to rats produces deficits in PFC attentional regulation that mimic the symptoms of attention-deficit hyper-activity disorder (ADHD)[152]. In humans, lead poisoning is associated with reductions in PFC grey matter153 and with various behavioural changes that arise from PFC dysfunction, including ADHD-like attentional and impulse-control problems, and even sociopathic, irresponsible and criminal behaviours154,155. lead poisoning highly correlates with crime rates and out-of-wedlock pregnancy in modern North America[154,155]. Interestingly, lead poisoning has also been proposed to have been the cause of the fall of the Roman empire, as the wealthy class ate foods preserved in lead syrup and ate from lead utensils[156]. The poor decision making and impulsive behaviours of the wealthy class — consistent with PFC dysfunction — led to the downfall of a great empire[156]. Thus, factors that dysregulate stress signalling pathways and weaken PFC structure and function can erode the civilized behaviour of entire cultures.

Conclusions and future directions

Tremendous advances have been made in understanding neurochemical influences on prefrontal function since the first landmark finding by Brozoski and colleagues 30 years ago[157], which showed that dopamine is essential for dorsolateral prefrontal working memory abilities. However, an immense amount of work remains to be done, including studies of additional neuromodulators, different prefrontal regions and other PFC cognitive operations. For example, important work is underway to reveal the complex and powerful effects on prefrontal functions of serotonin, another modulator that is released in the PFC during exposure to uncontrollable stress[158] and that is key to orbital PFC function[159]. Serotonin is particularly relevant to the aetiology and treatment of depression, and genetic alterations in serotonin receptors or the serotonin transporter can influence PFC limbic connections[160]. However, little is known about how serotonin alters PFC cell firing in animals performing tasks that involve the PFC. one study has shown that high levels of $5-HT_{2A}$ receptor stimulation can suppress dorsolateral PFC neuronal firing in monkeys performing a working memory task[161]. These results are similar to those observed with high levels of stimulation of the α_1-adrenergic receptor which, like the $5-HT_{2A}$ receptor, is coupled to phosphatidylinositol–PKC signalling. A recent study in rats suggests that serotonin stimulation of $5-HT_{2C}$ receptors impairs reward reversal[162], a function that is highly

dependent on the orbital PFC. It would be fascinating to investigate whether 5-HT_{2C} receptor stimulation would suppress the firing of orbital PFC neurons in monkeys performing a reward reversal task, and whether these effects could be blocked by agents that inhibit phosphatidylinositol–PKC signalling.

The detrimental effects of stress on PFC networks are particularly problematic in the 'information age', when PFC-mediated cognitive abilities are increasingly needed for success. understanding the molecular mechanisms that alter PFC structure and impair PFC function during stress exposure will help to reveal how genetic and environmental insults can increase an individual's susceptibility to PFC deficits. Identifying the molecular mechanisms that alter PFC function will provide the foundation for a new era in psychiatry, when we will understand how genetic changes affect intracellular signalling, neural development and neurophysiology in the circuits that underlie neuropsychiatric symptoms. It is hoped that this information will provide the framework for therapies aimed at rectifying molecular errors and ameliorating the symptoms of mental illness.

Glossary

Attentional set	A predisposition to attend to one dimension of a stimulus while inhibiting other dimensions — for example, attending to colour rather than shape.
Trier social stress test	A test in which subjects have to give a speech and perform calculations in front of a panel of people they do not know. Blood or saliva samples and blood pressure measurements can be taken before, during and after the test to determine the physical response to the stressor.
Learned helplessness paradigm	A paradigm developed more than 30 years ago in which rats were exposed to inescapable shock, and supposedly learned that they were helpless to respond. Research has debunked this interpretation and instead determined that uncontrollable stress can cause cognitive deficits.
Y-maze task	A task in which rats must learn to escape from a Y-shaped maze by making the correct decision. Exposure to uncontrollable stress and the presence of task-irrelevant cues in the maze has been found to impair performance.
Spatial delayed alternation task	A test of spatial working memory for primates or rodents in which the subject is required to make alternate responses on successive trials, with a delay period interposed between trials.
Tuned persistent firing of neurons	The neuronal representation of a specific stimulus — for example, a cue in a specific spatial location. Owing to network connections, a cell can sustain firing without stimulation from the environment, but the sustained firing (in this example) occurs only following a cue to a specific location in space; thus the neuron is 'tuned' to that direction.
Phosphodiesterase	An enzyme that hydrolizes cAMP. Inhibition of phosphodiesterase leads to a build-up in cAMP concentrations.

Acknowledgments

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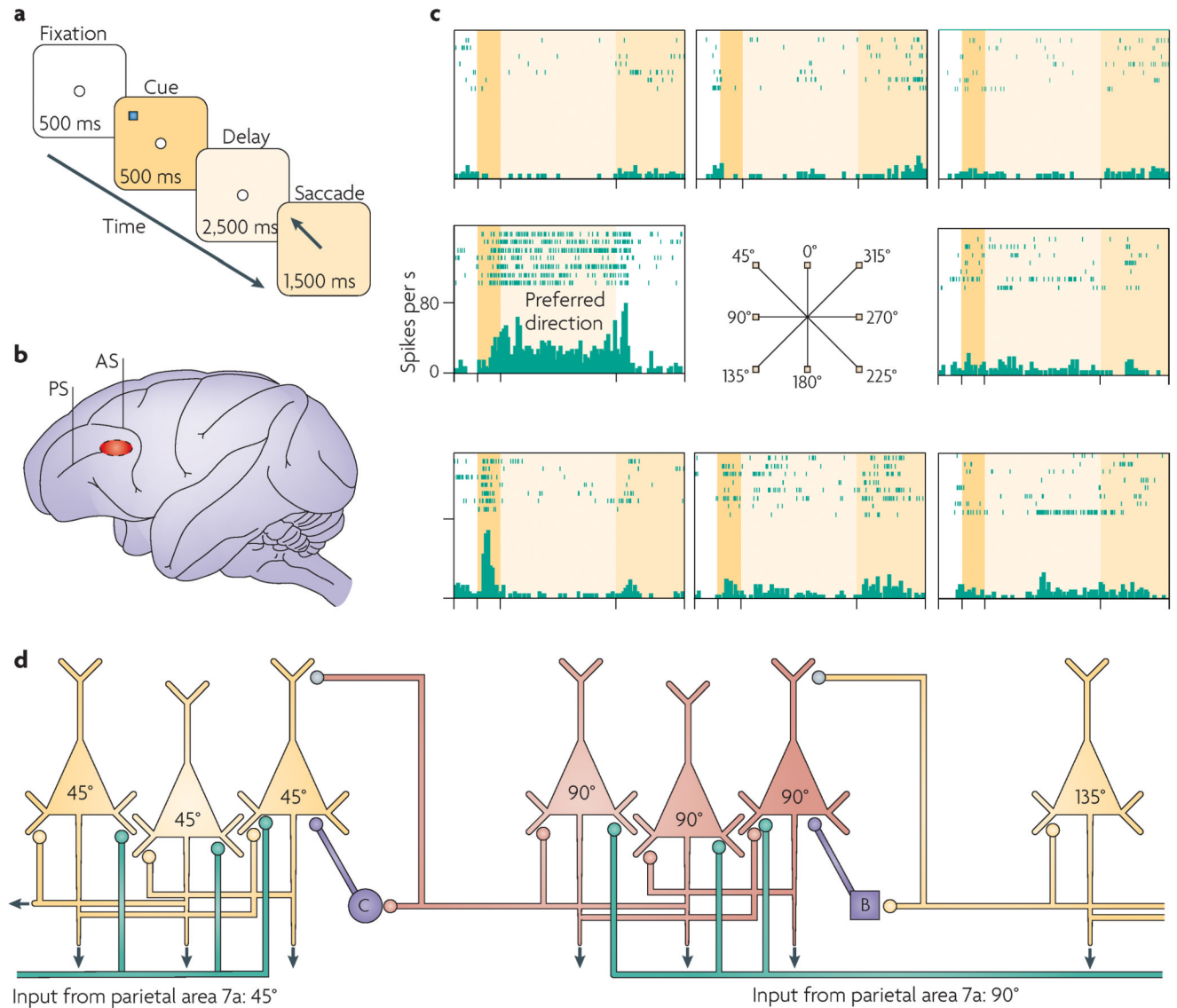
Figure 1. Spatial working memory networks in the dorsolateral prefrontal cortex

a | The oculomotor delayed response (ODR) task is a spatial working memory task that is used to probe the physiological profiles of prefrontal cortex (PFC) neurons. The subject must remember the spatial position of the most recent cue over a delay period of several seconds and then indicate that position with a saccade to the memorized location. **b** | The region of the monkey dorsolateral PFC (Walker's area 46) where neurons show persistent, spatially tuned firing during the delay period in the ODR task. **c** | An example of a PFC neuron that showed persistent firing during the delay period if the cue had occurred at 90° — the 'preferred direction' for this neuron (left middle plot) — but not if the cue appeared in a 'non-preferred' direction (other plots). The rasters show the firing of the neuron over seven trials at each spatial position. **d** | A schematic drawing of the PFC microcircuits that underlie spatial working memory as described by Goldman-Rakic[40]. Layer III pyramidal cells receive highly processed spatial information (represented by the green lines) from parietal association cortices. Pyramidal cells with similar spatial characteristics engage in recurrent excitation to maintain persistent activity over the delay period (note that the subcellular localization of these excitatory connections is not currently known; they could be

on the apical and/or basal dendrites). GABA (γ-aminobutyric acid)-ergic interneurons, such as basket cells (B) and chandelier cells (C) help to spatially tune neurons through lateral inhibition. Inputs from cross-directional microcircuits (neurons with different tuning characteristics) are shown in grey. AS, arcuate sulcus; PS, principal sulcus. Parts **a–c** are modified, with permission, from REF. [60] ©(2007) Cell Press.
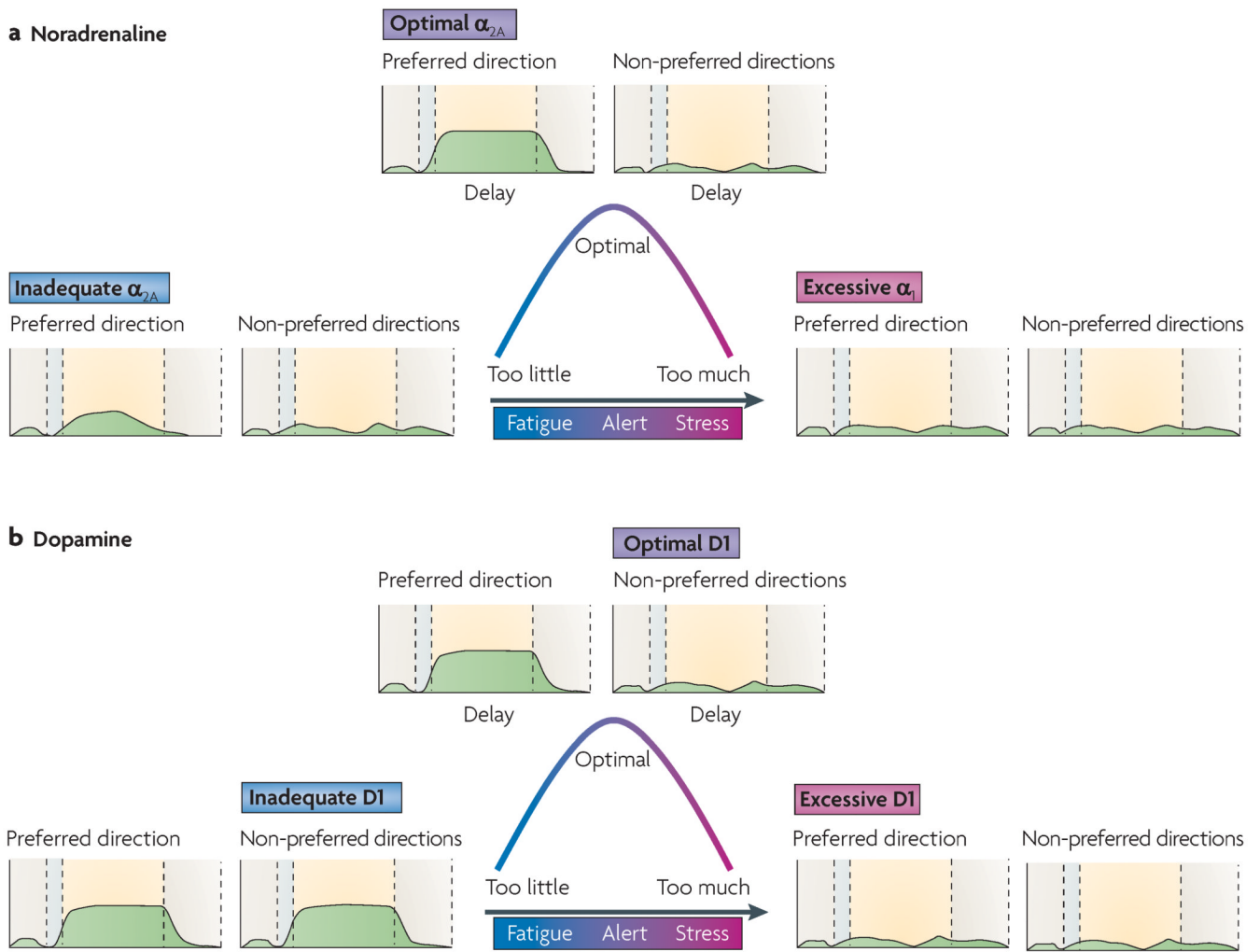
Figure 2. Catecholamine influences on prefrontal cortex physiology and function
Both noradrenaline (NA, part **a**) and dopamine (DA, part **b**) have 'inverted U-shaped'
influences on prefrontal cortex (PFC) physiology and cognition, whereby either too little or
too much of the neurotransmitter impairs PFC function. In an oculomotor delayed response
task, with optimal levels of NA or DA release under alert, non-stressed conditions (top of
the curves), PFC neurons fire (as shown in the green traces) during the delay period
following cues for preferred but not non-preferred directions. NA enhances delay-related
firing in response to cues in preferred directions by stimulating α_{2A}-receptors (increasing the
'signal'), whereas DA weakens delay-related firing in response to cues in non-preferred
directions by stimulating D1 receptors (decreasing the 'noise'). Administration of
appropriate concentrations of the α_{2A}-receptor agonist guanfacine or the D1 receptor agonist
SKF81297 also has this effect. With high levels of NA release during stress (right side of the
curve), NA engages the lower-affinity α_1-receptors and so reduces neuronal firing.
Similarly, excessive D1 receptor stimulation during stress suppresses cell firing.
Administration of the α_1-receptor agonist phenylephrine or a high concentration of
SKF81297 can mimic the effects of high NA and DA levels, respectively. In each graph,
the dotted lines indicate the transition between (from left to right) the fixation period, the
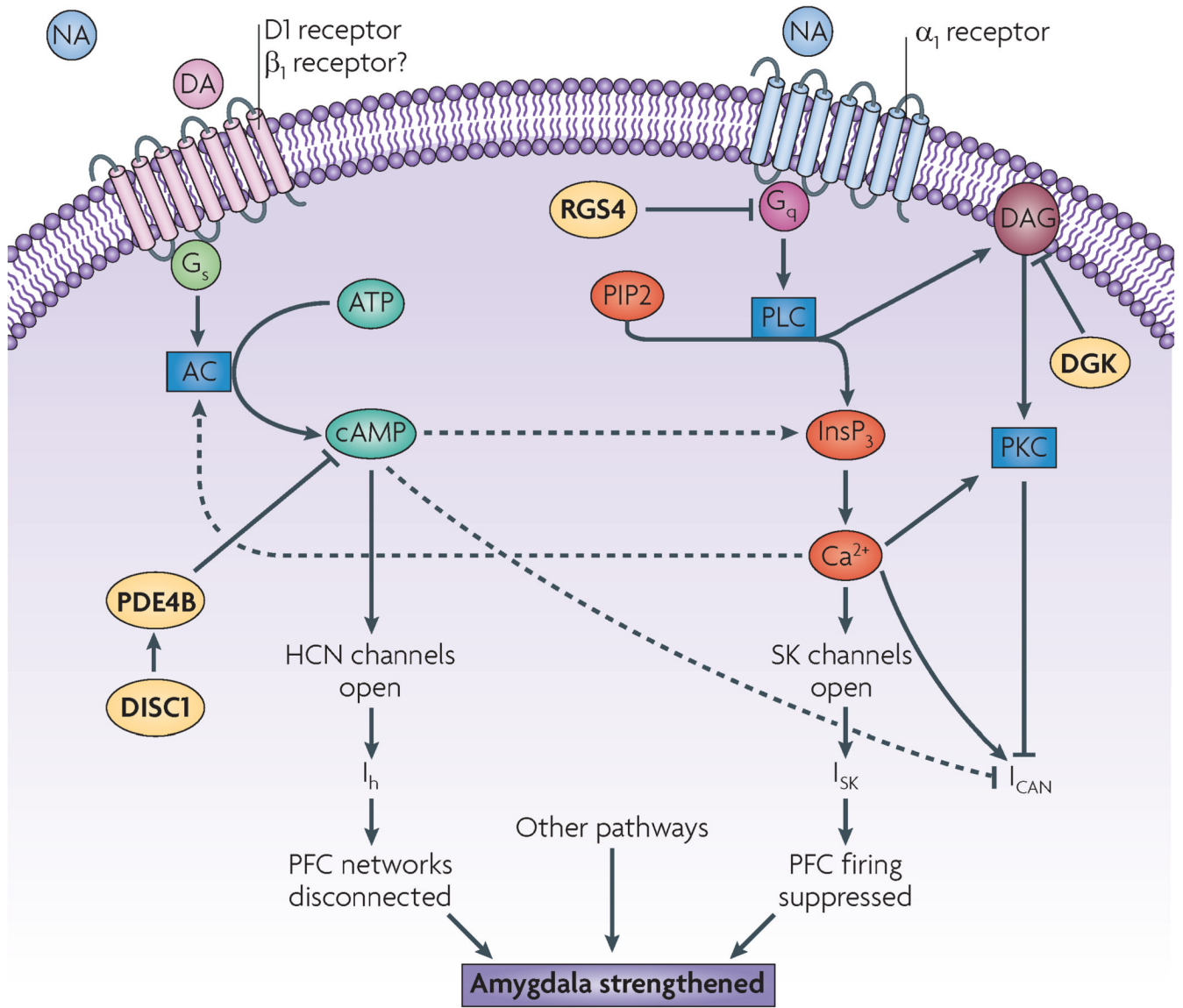cue period, the delay period and the oculomotor response period.

Figure 3. Intracellular signalling pathways that impair prefrontal cortex working memory functions during stress

Intracellular signalling pathways activated by stress exposure have feedforward interactions that rapidly impair prefrontal cortex (PFC) cognitive function. High levels of dopamine (DA) D1 receptor stimulation (and probably noradrenaline (NA) β_1-receptor stimulation as well) activate adenylyl cyclases (ACs) to produce cyclic AMP. cAMP opens hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN channels) on dendritic spines to produce the h current (I_h), which weakens network inputs and decreases delay-related firing. High levels of NA also stimulate α_1-receptors, which activate phosphatidylinositol biphosphate (PIP2)–protein kinase C (PKC) signalling. Subsequent inositol-1,4,5-trisphosphate (InsP$_3$)-mediated Ca^{2+} release has been shown to reduce PFC cell firing by opening SK channels, leading to a current (I_{SK}), and has been shown to maintain firing through the depolarizing current I_{CAN}. I_{CAN} can be reduced by PKC and cAMP, such that the suppressive effects of I_{SK} probably predominate under conditions of stress. The two signalling pathways interact to potentiate each other's actions (dotted

arrows); for example, cAMP can potentiate InsP$_3$-medicated Ca^{2+} release through protein kinase A-mediated phosphorylation of InsP$_3$ receptors. Conversely, Ca^{2+} can activate many isoforms of AC to generate more cAMP. Glucocorticoids might also activate these pathways (see main text). Enzymes that normally provide the molecular brakes on these stress signalling pathways (disrupted in schizophrenia 1 (DISC1), regulator of G-protein signalling 4 (RGS4) and DAG kinase (DGK)) are often genetically altered in families with serious mental illness, thus increasing susceptibility to stress exposure. Note that the cAMP and PKC signalling pathways have also been shown to be activated in the amygdala during stress, where they strengthen long-term memory consolidation and fear conditioning. DAG, diacyglycerol; PDE4B, phosphodiesterase 4B.
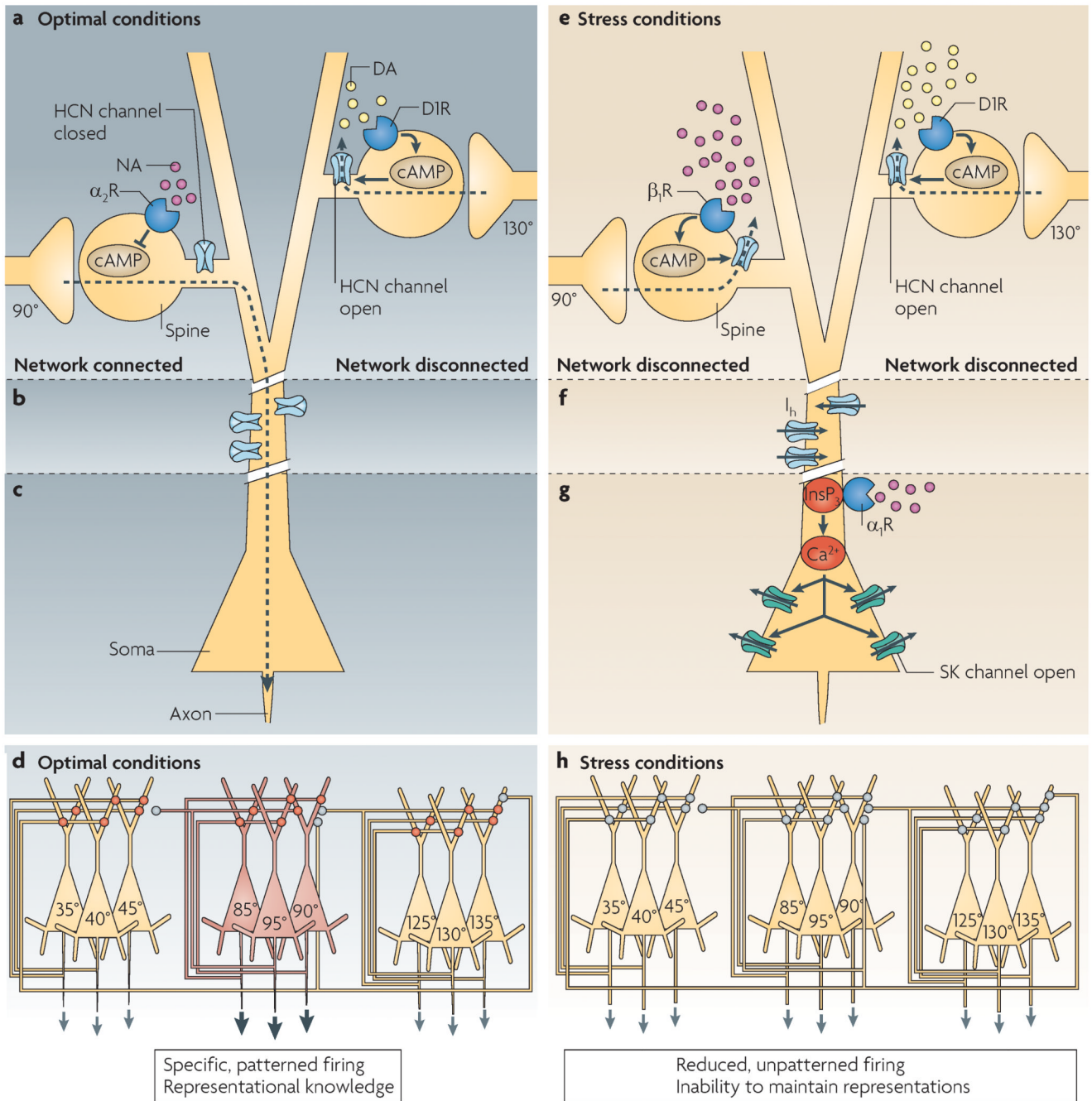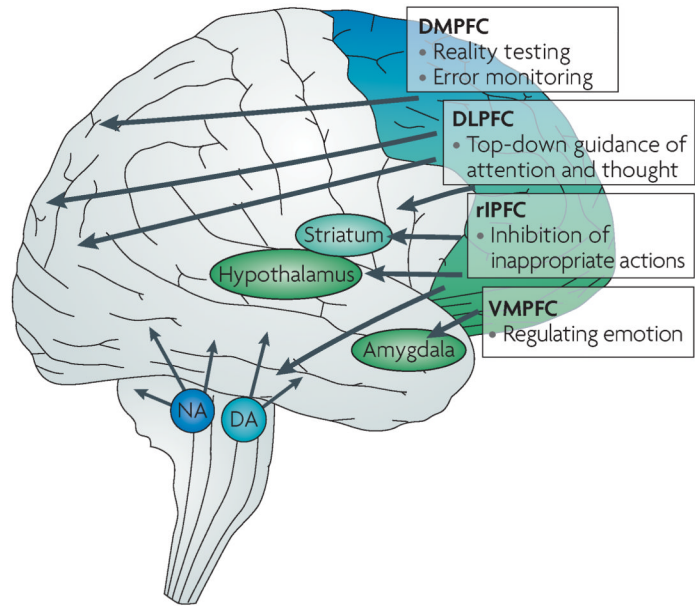
Figure 4. A working model showing how prefrontal cortex pyramidal cell activity might be regulated under optimal versus stress conditions

a | The efficacy of network inputs onto dendritic spines of the apical and/or basal dendrites is dynamically regulated by cyclic AMP–hyperpolarization-activated cyclic nucleotide-gated cation channel (HCN channel) signalling. Under optimal conditions, appropriate network connections are strengthened by α_{2A}-receptor inhibition of cAMP–HCN channel signalling, whereas inappropriate network connections are weakened by dopamine D1 receptor activation of cAMP–HCN channel signalling. The small volume of the spine compartment probably allows very localized regulation of nearby HCN channels. The resulting specific pattern of network connectivity allows accurate representation of the cue's spatial position

in the oculomotor delayed response task, and the breadth of connectivity can be dynamically regulated based on current cognitive demands. **b** | HCN channels on the plasma membrane of dendritic shafts probably regulate excitability. They might not be open when the dendrite is depolarized by large numbers of excitatory network connections. **c** | Under optimal conditions, the cell body probably receives network signals and fires accordingly. **d** | Under optimal conditions the PFC shows highly patterned activity, whereby specific subsets of neurons are active to represent the precise spatial position of a stimulus. This is denoted in the figure, in which only the microcircuit representing 90° is active. Note that interneurons are not shown in this diagram for the sake of clarity. Network inputs are shown on the apical dendrites, but they might actually be on basal dendrites. Red circles represent α_{2A}-receptor strengthening of network inputs; grey circles represent D1 receptor–cAMP weakening of a network connection. **e** | Under conditions of stress, high levels of cAMP open HCN channels throughout the dendrite, weakening all network connections. **f** | With loss of network excitatory inputs the dendrite might hyperpolarize, and HCN channels on dendritic shafts might open to help maintain dendritic excitability. HCN channel opening would also reduce the effectiveness of inputs onto the distal portions of the dendrite. **g** | High levels of phosphatidylinositol signalling during stress would increase inositol-1,4,5-trisphosphate (InsP$_3$)-mediated waves of intracellular Ca^{2+} release. When the Ca^{2+} waves invade the soma, they open small-conductance, Ca^{2+}-activated K^+ channels (SK channels) and reduce cell firing. **h** | Under stressful conditions, network connections are weakened (grey circles) and, as a result, network firing is reduced and unpatterned. Thus, prefrontal cortex neurons are unable to accurately represent information in working memory. Unpatterned, generalized activity might serve another function — for example, stimulating stress pathways in the brainstem.

a Prefrontal regulation during alert, non-stress conditions

DMPFC
• Reality testing
• Error monitoring

DLPFC
• Top-down guidance of attention and thought

rlPFC
• Inhibition of inappropriate actions

VMPFC
• Regulating emotion

Striatum

Hypothalamus

Amygdala

NA   DA

b Amygdala control during stress conditions

Loss of prefrontal regulation

Emotional habits

Striatum

Hypothalamus

Bottom-up attention

Amygdala

Emotional associations

NA   DA

Emotional reflexes

figure.