Cellular and Molecular Life Sciences

REVIEW

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Neuronal correlates of depression

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Abstract Major depressive disorder (MDD) is a common psychiatric disorder effecting approximately 121 million people worldwide and recent reports from the World Health Organization (WHO) suggest that it will be the leading contributor to the global burden of diseases. At present, the most commonly used treatment strategies are still based on the monoamine hypothesis that has been the predominant theory in the last 60 years. Clinical observations show that only a subset of depressed patients exhibits full remission when treated with classical monoamine-based antidepressants together with the fact that patients exhibit multiple symptoms suggest that the pathophysiology leading to mood disorders may differ between patients. Accumulating evidence indicates that depression is a neural circuit disorder and that onset of depression may be located at different regions of the brain involving different transmitter systems and molecular mechanisms. This review synthesises findings from rodent studies from which emerges a role for different, yet interconnected, molecular systems and associated neural circuits to the aetiology of depression.

Abbreviations

3V	Third ventricle
4V	Fourth ventricle
5-HT	Serotonin
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Arc	Activity-regulated cytoskeleton-associated protein gene
BDNF	Brain-derived neurotrophic factor
BLA	Basolateral amygdala
Ca^{2+}	Calcium
CaMKII	Calcium/calmodulin-dependent protein kinase II
CeM	Central amygdala
CPP	3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid
CRF	Corticotrophin-releasing factor
CSD	Chronic social defeat
CUS	Chronic unpredictable stress
D1	Dopamine 1 receptor
D2	Dopamine 2 receptor
D3V	Dorsal third ventricle
DBS	Deep brain stimulation
delta FosB	Delta FBJ murine osteosarcoma viral oncogene homolog B
DMH	Dorsomedial nucleus of the hypothalamus
DNMT	DNA methyltransferase
DRN	Dorsal raphe nucleus

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eEF2	Eukaryotic elongation factor
Egr1	Early growth response protein 1 gene
ERK1/2	Extracellular signal regulated kinase
FosB	FBJ murine osteosarcoma viral oncogene homolog B
G9a	Histone H3 lysine 9 methyltransferase
GABA	Gamma-aminobutyric acid
GLP	Histone H3 lysine 9 methyltransferase
GluR1	Glutamate receptor subunit 1
GluR2	Glutamate receptor subunit 2
GluR3	Glutamate receptor subunit 3
GPo	Globus pallidum
H3K9me2	Histone H3 dimethyl Lys9
HATS	Histone acetyltransferase
HCN	Hyperpolarisation-activated cyclic nucleotide-gated channel
HDAC	Histone deacetylase
HDM	Histone demethylase
HMT	Histone methyltransferase
I_h	Hyperpolarisation-activated non-selective cation current
IKK	I_{KB} kinase
IKKdn	IKK dominant negative
IVF	In vitro fertilisation
K^+	Potassium
LC	Locus coeruleus
LDTg	Laterodorsal tegmental nucleus
LH	Lateral hypothalamus
LHb	Lateral habenula
LTD	Laterodorsal tegmentum
MAPK	Mitogen-activated protein kinases
MDD	Major depressive disorder
mGluR2	Metabotropic glutamate receptor 2
MK-801	5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine
mper1/2	Period gene 1 and 2
mPFC	Medial prefrontal cortex
MSN	Medium spiny neurons
mTOR	Mammalian target of rapamycin
NAc	Nucleus accumbens
NF_{kB}	Nuclear factor kB
NMDAR	N-methyl-D-aspartate receptor
NR2B	NMDAR 2B subunit
PPTg	Pedunculopontine tegmental nucleus
REM	Rapid eye movement
RMTg	Rostromedial tegmental nucleus
SC1	Sparc-like 1
SCN	Suprachiasmatic nucleus
SD	Sleep deprivation
SDT	Sleep deprivation therapy
SN	Substantia nigra
SPZ	Subparaventricular zone

SSRI	Serotonin selective reuptake inhibitor
SUV39H1	Histone-lysine N-methyltransferase
vHIP	Ventral hippocampus
VP	Ventral pallidum
VSCC	Voltage sensitive calcium channels
VTA	Ventral tegmental area
WKY	Wistar Kyoto
ZFP	Zing-finger protein

Introduction

Major depressive disorders (MDD) are projected to become the leading contributor to the global burden of disease according to the world health organisation (WHO) and other studies [1–3]. There have been dramatic advances in the treatments for various diseases that target the immune and cardiovascular systems. In comparison, treatments for depressive disorders, predominantly based on the monoamine hypothesis, still relies on approaches developed over 60 years ago [4, 5]. Depression is a diverse and complex mental illness with different antecedent causes and manifestation of symptoms. The major drawback of classical antidepressant treatment is that less than 50 % of patients respond positively to current antidepressant medications while alleviation of depressive symptoms can take weeks or months for those who do respond to treatment [6, 7]. The limited understanding of the neural circuitry and molecular mechanisms involved in depression is one of the key reasons for the lack of more effective treatments. Recent groundbreaking studies showing rapid alleviation of depression with deep brain stimulation (DBS) strongly suggests that depression is a neural circuit disorder [8–11]. Advances in molecular studies have highlighted the role of specific molecular signalling and epigenetic changes and the associated modifications in neuronal development of depression [12–17]. It is likely that these differential molecular and functional responses in various brain regions may be responsible for the wide spectrum of symptoms observed in depressive patients.

Studies in depression have benefited from the availability of various technical approaches enabling researchers to investigate molecular changes at the level of the single cell while others take a more expansive systems-level approach to investigate functional changes at the level of the neural circuit. In this review article, we try to highlight the major points to give the reader a flavour of the current standings in different aspects of research in depression. Since various biological processes effect different systems such that, for example, molecular changes can then lead to changes in neural circuit activity, it will be evident that description of certain processes will overlap

with other sections within the review. We begin this review by first describing evidence for molecular changes linked to depression followed by genetic modifications and associated neurogenesis leading to structural changes associated with depression-related synaptic plasticity. We then focus on the more expansive studies showing evidence for the role of the immune system in depression followed by findings from systems-level approaches describing functional changes of the neural circuit in depression. Finally, we further emphasise functional circuit-level complexity of depression by describing the role of two distinct regions of the brain, the circadian and sleep/wake centres, in depression.

Molecular signalling

Brain-derived neurotrophic factor (BDNF) has numerous functions in the developing and mature brain [18, 19]. Among these is signalling within the mesolimbic brain reward centre, ventral tegmental area-nucleus accumbens (VTA-NAc) dopaminergic circuit, in encoding for depression related behaviour. For example conditional deletion of BDNF expression in the VTA, but not NAc, prevents the development of social defeat stress-induced behavioural abnormality [12, 20]. Furthermore, evidence suggests that the increase in BDNF signalling in the VTA-NAc circuit is stress-context dependent since the phasic activity of VTA-NAc dopamine neurons leads to increased BDNF levels in the NAc of social stress experienced, but not stress naïve mice [21]. In the NAc the stress induced neuropeptide corticotropin-releasing factor (CRF) is functional at both the pre- and post-synaptic terminals [22], and increased CRF signalling in the NAc increases motivation for cued rewards [23]. It is hypothesised that stress-induced CRF gates BDNF signalling in the NAc [21]. In this model, CRF signalling in NAc activates its receptors located presynaptically on VTA DA neurons and works together with arriving phasic spikes from these DA neurons to release BDNF unto medium spiny neurons (MSNs) in the NAc. In addition to the NAc, exposure to stress increases BDNF levels in the amygdala in a time dependent manner [24, 25]. BDNF mRNA levels were shown to be increased in the BLA and CeM, but not medial amygdala, 2-h following stress exposure while 24-h post-stress exposure BDNF levels were shown to be reduced [24, 26, 27]. In contrast, decreased BDNF levels were found in the postmortem amygdala of female subjects with MDD [28]. The differential temporal expression of BDNF mRNA expression indicates that stress-induced changes in BDNF expression are transient in the amygdala. Evidence supports the notion that the role of BDNF in mood disorders varies between different brain regions. For example, elevated NAc BDNF

increases the depressive phenotype, while findings from the hippocampus and PFC indicate increased BDNF levels reverses the depressive phenotype. In humans studies, lower levels of BDNF were found in the hippocampus and PFC of subject who had committed suicide while levels were elevated in patients treated with antidepressants [29–32]. Recent studies further confirmed that chronic antidepressant treatment increases BDNF and TrkB receptor mRNA expression in the hippocampus [33]. In contrast, post-mortem analysis of depressed patients found higher levels of BNDF in the NAc [12]. Though the mechanism of how antidepressant treatment increases BDNF-TrkB expression is unknown, a possible mechanism may involve increased monoaminergic transmission [33, 34]. Findings that antidepressants induced increases in BDNF overlaps closely with increases in both CREB mRNA expression and CREB-phosphorylation state within the hippocampus have led to the suggestion that CREB may contribute to the antidepressant-induced increase in BDNF expression [33]. The mechanisms of action of BDNF in the context of depression in these various brain regions are still unclear. The differential interaction of pre- and post-synaptic BNDF-TrkB pathway with various intra and extracellular signalling systems such as second messenger pathways (including phospholipase C, PI3K and MAPK/ERK pathways), inflammatory cytokines, excitatory glutamatergic neurotransmitters and stress hormones could in part result in the contrasting observations of BDNF levels in the different regions of the brain in relation to depression [35].

Previous studies have implicated changes in the level of the intracellular signalling molecule calcium/calmodulin-dependent protein kinase II (CaMKII) following stress and antidepressant responses [36–38]. βCaMKII is known to regulate activity of various intracellular pathways and channels that regulate neuronal activity [39]. The lateral habenula (LHb) is an evolutionary conserved nucleus that integrates inputs from various limbic forebrain and motor systems involved in regulating motivational behaviours [40]. Furthermore, aberration in LHb function has been implicated in depression [41–43]. Recent evidence has shown that stress-induced increased activity of LHb neurons is the result of up-regulation of βCaMKII activity leading to increased membrane insertion of the excitatory glutamate receptor GluR1 [44]. In contrast, treatment with antidepressants down-regulated CaMKII expression in the LHb [44].

Clinical studies consistently demonstrate that a single sub-psychotomimetic dose of Ketamine, an ionotropic glutamatergic NMDAR (N-methyl-D-aspartate receptor) antagonist, produces rapidly acting antidepressant responses in patients suffering from depression [45–47]. Ketamine and other NMDAR antagonists together with metabotropic GluR2/3 receptor antagonists also produce

rapid antidepressant-like effects in mouse behaviour [48–50]. By determining the degree of immobility, a measure of helplessness associated with the depressive phenotype, in the forced swim test (FST) paradigm, NMDAR antagonist ketamine, CPP and MK-801 were shown to alleviate depressive behaviour within 30 min of drug administration [48]. The antidepressant effects of ketamine lasted 24-h post administration, much longer than its 2-h half-life, indicating that ketamine induces longer-term changes. In line with its putative role in inducing longer-term plastic changes, administration of ketamine increased BDNF levels in the hippocampus [48]. How is it that blocking excitatory NMDAR activity elicits plasticity in the hippocampus? Prior work had demonstrated that NMDAR block maintains eukaryotic elongation factor (eEF2) in the dephosphorylated (active) state [13]. Mechanistically, ketamine blockade of NMDA receptors deactivates CaM-KII (also known as eukaryotic elongation factor 2 kinase—eEF2k) activity and the subsequent decrease in phosphorylation of eEF2 leads to rapid hippocampal BDNF synthesis by removal of baseline phosphorylated-eEF2 suppression of BDNF synthesis [48, 51, 52]. The antidepressant actions of ketamine are blocked by pretreatment with glutamate-AMPA receptor antagonist [53]. Detailed analysis showed that acute suppression of NMDA receptor mediated spontaneous neurotransmitter release leads to rapid BDNF protein synthesis resulting in increased AMPA receptors surface expression and subsequent increases in potentiation of synaptic responses in the hippocampus [52]. Activation of NMDA receptors is believed to regulate mTOR activity via a variety of putative intracellular signalling mechanisms such as the phosphatidylinositol 3 kinase—AKT (PI3K-AKT) and calcineurin pathways [54–56]. The mammalian target of rapamycin (mTOR) signalling pathway is a serine/threonine kinase, that regulates the initiation of protein translation, is expressed in dendritic development that controls new protein synthesis [57, 58]. Changes in activity of various signalling processes such as BDNF, NMDA and their downstream target mTOR are possible mechanisms that underlie changes in synaptic plasticity leading to depression [59]. For example, changes in homeostatic plasticity in regions such as the PFC are putatively linked in part to aberrations in mTOR signalling, which has been hypothesised to lead to the expression of the depressive phenotype [59]. Convergent evidence over the past 20 years indicates that prolonged stress leads to overall neuronal atrophy and synaptic depression in the PFC and hippocampus [59–62] while regions such as the amygdala and NAc exhibit changes consistent with neuronal hypertrophy and synaptic potentiation [59, 63, 64]. Why stress induces opposing effects in different brain regions is still unclear and much more work is required to delineate these molecular differences. Some of the

pathways involving stress-induced changes in BDNF and NMDA-mTOR signalling have been better studied in the PFC. For example, synaptic deficits in the PFC following stress has been shown to be precipitated by a initial increase in glutamate release and reduced glutamate uptake leading to increased glutamate excitotoxicity, thus resulting in neuronal atrophy through dendritic retraction, reduced dendritic arborisation, decreased spine density and reduced synaptic strength [59]. Emergence of such synaptic dysconnectivity can potentially lead to the reduction of neurotrophic factors such as BDNF and the overall decrease in NMDA signalling and the inhibition of mTOR signalling that subsequently leads to the expression of depressive-like behaviour [59, 65, 66]. This putative mechanism by which stress induces synaptic changes in the PFC highlights the significance of cortical mTOR signalling underlying ketamine-mediated antidepressant responses [67, 68]. Thus, at the micro-circuit synaptic level, a possible mechanism, by which Ketamine-induced NMDA blockade can reverse depressive behaviours may initially involve inhibition of pre-synaptic NMDA receptors at GABAergic interneurons leading to decreased inhibitory tone and subsequent net increase in glutamatergic surge; while inhibition of, excitotoxic, extrasynaptic NMDA receptors on the post-synaptic neurons increases cell survival. Furthermore, increased net glutamatergic surge leads to increased postsynaptic AMPA receptor activation of neuroplasticity-related signalling pathways involving BDNF and mTOR, resulting in overall synaptogenesis and synaptic potentiation [48, 59, 68, 69]. The complex interactions between various pathways are evidenced by findings that activation of L-type voltage sensitive calcium channels (VSCC) resulted in AMPA receptor stimulation leading to mTOR pathway activation [70]. In line with this, pretreatment with L-type VSCC antagonist blocked the antidepressant effects of ketamine [71]. Hence, another possible mechanism by which ketamine induces antidepressant effects may involve activation of both L-type VSCC and AMPA receptors subsequently leading to downstream activation of the mTOR pathway.

The neuroendocrine system consisting of the hypothalamic-pituitary-adrenal axis (HPA axis) controls reactions to stress and is involved in homeostatic regulation of processes such as digestion, immune system, mood and emotions, energy storage and expenditure. The HPA axis plays a pivotal role in regulating physiological responses induced by stress events where its activation prepares the body for the fight/flight response. Depression and anxiety disorders are often characterised by altered HPA-axis [72–74]. During periods of stress the HPA axis releases corticotrophin-releasing hormone (CRH) from the hypothalamus, which stimulates adrenocorticotropin (ACTH) hormone secretion from the anterior pituitary, which then stimulates secretion

of cortisol and other glucocorticoids from the adrenal cortex. Chronic (long-term), but not acute (short-term), unpredictable stress paradigm induced impairment in adrenal medullary function as measured by robust decreases in numerous proteins such as catecholamines, and SNARE proteins [75]. Increased cortisol concentration in plasma, urine and cerebrospinal fluid, and exaggerated cortisol response to ACTH has been reported in MDD patients [76–79]. Furthermore, increased levels of CRH have been found in cerebrospinal fluid, locus coeruleus and PFC of depressed and suicide patients [79–83]. Animal studies strongly corroborate the role of the HPA axis in depression where early life stressors such as maternal separation induce increased CHR mRNA expression in hypothalamic, paraventricular nucleus, central nucleus of the amygdala, bed nucleus of the stria terminalis and locus coeruleus [84]. Direct ACTH administration increased both the serum cortisol levels and the depressive phenotype as measured by the forced swim test and latency to feed in a novelty suppressed feeding test [85]. Furthermore, ACTH administration decreased hippocampal BDNF levels, evidence that correlates well with observations of decreased BDNF levels in the hippocampus of animals expressing the depressed phenotype. As will be discussed later mood disorders are associated with disruptions in homeostatic plasticity and associated with this, recent data suggest that stress changes neural connections. Chronic stress reduces spine density in hippocampus, mPFC, medial amygdala, while in the basolateral amygdala spine density was increased [86, 87]. Glucocorticoids exert both direct and non-direct genomic effects that can regulate intracellular signalling and synaptic plasticity [87]. Acute cortisol challenges given to stress naïve or chronically stressed rats revealed highly differential gene profiles depending on the stress history of the animals, where 200 of the genes altered by cortisol was similar in both groups of rats; however, 500 genes were differentially altered following chronic stress [87, 88]. These findings would indicate that though the brain is able to recover following exposure to acute stress, stress history leads to changes that alter future molecular reactivity to subsequent stress that may increase susceptibility to depression. Recent findings have shown that the levels of presynaptic auto-inhibitory mGluR2 receptors are decreased in stress susceptible mice and that the antidepressant drug acetyl-L-carnitine, via epigenetic mechanisms, induces expression of presynaptic mGluR2 receptors leading then to the normalisation of glutamate transmission and the subsequent reversal of the depressive phenotype [89]. A recent follow up study showed differences in mGluR2 expression following CUS exposure where hippocampal mGluR2 expression was decreased only in stress susceptible mice while PFC mGluR2 expression was decreased in both stress resilient and stress susceptible mice [90]. In addition, evidence for the differential effects of

stress duration was observed where mice exposed to acute stress still exhibited decreased hippocampal mGluR2 expression but no effect was observed in the PFC [90]. Furthermore, mineralocorticoid receptor, but not glucocorticoid, levels in the hippocampus were lower in stress resilient mice while there was no difference in the PFC [90]. Using pharmacological methods, the authors postulate that glucocorticoid activation regulates mGLuR2 expression via mineralocorticoid receptor activation [90]. The differential molecular response in mGlu2 expression in stress resilient and susceptible mice further highlights the complex responses to stressors in varying regions of the brain. Furthermore, a better understanding of the interaction within the neuroendocrine system in stress will help elucidate novel therapeutic targets for antidepressant treatment. The complexity of biochemical cross-talk at the molecular level further highlights potential variability in the activation of signalling pathways in various brain regions and circuits that may underlie the large variation in symptoms of depressive patients.

Epigenetic mechanisms

Genetics alone does not account for MDD due to the high discordance rate (50 %) observed in monozygotic twins [91]. Environmental factors, particularly exposure to stressful life events increases the likelihood of the onset of depression [92, 93]. However, most people exposed to environmental stress do not exhibit MDD [94]. This variability in vulnerability to environmental stress has lead to the hypothesis that epigenetic mechanisms may determine risk for depression throughout life [95]. Epigenetics is a molecular phenomenon describing heritable changes in gene expression that does not involve changes in DNA sequence [96]. Briefly, DNA wrapped around histone protein makes up the nucleosome—the unit of chromatin. Genes within tightly spaced nucleosomes are actively transcribed while genes within tightly packed nucleosomes are silenced. Complex post-translational processes such acetylation or methylation on histone tails lead to changes in nucleosome spacing that result in modulation of gene expression [97]. Histone acetylation, catalysed by histone acetyltransferase (HATS) and reversed by histone deacetylase (HDACs), generally drives an open state of the chromatin resulting in increased gene expression. Histone methylation, catalysed by histone methyltransferase (HMTs) and reversed by histone demethylase (HDMs), can activate or reverse gene expression. In addition, DNA methylation, catalysed by DNA methyltransferase (DNMTs) generally, but not always, drives gene repression. Post-translational modification of these acetylation and methylation are carried out by numerous 'reader' and

'eraser' proteins resulting in change of chromatin structure and gene transcription [96, 97]. Growing evidence supports the hypothesis that epigenetics is a mechanism by which exposure to environmental stimuli such as stress lead to changes in gene expression in vulnerable, genetically predisposed, individuals resulting in MDD. One of the earliest studies to report epigenetic modifications in an animal model of depression demonstrated transient decrease followed by persistent increase of histone acetylation in the NAc following chronic social defeat (CSD) stress [98]. Furthermore, direct infusion of HDAC inhibitors reversed the depressive phenotype in previously depressive mice [98]. More recently, conditional inhibition of HDAC2 function in the NAc induced the stress-resilient phenotype in mice exposed to chronic stress [99]. Conversely, decreasing HDAC5 function leads to a stronger expression of depressive-like behaviour following CSD stress [100]. In contrast, HDAC5 expression was significantly elevated in the hippocampus of rats following chronic mild stress [101]. Epigenetic changes exhibit differing temporal dynamics in different brain regions following exposure to CSD stress. For example, in the hippocampus of stress-susceptible mice histone acetylation is initially increased followed by a persistent decrease [102] while in the NAc increased histone acetylation was observed [100]. Levels of histone methyltransferase G9a, GLP and SUV39h1 was decreased in the NAc of mice susceptible to CSD stress, while in resilient mice the levels were increased [103]. Furthermore, overexpression of G9a in the NAc exerted antidepressant-like behaviours, whereas knockdown of G9a induced pro-depressant-like effects [103]. A more recent study using engineered transcription factors (zinc finger proteins—ZFP) to site selectively remodel chromatin found that ZFP-induced enrichment of H3K9me2 at *fosb* gene in the NAc reduced both *fosb/delta fosb* expression and also induced anxiety and depressive-like behaviours following subthreshold social defeat stress [104]. Classical antidepressant medications, such as selective serotonin reuptake inhibitor (SSRI), imipramine was shown to increase NMDA receptor 2B (NR2B) subunit expression via mechanisms involving increased histone acetylation on the NR2B promoters and decreased activity of HDAC [105]. As mentioned previously expression of neurotropic factor BDNF is implicated in animal models of depression [12, 20]. Recent clinical studies have extended these findings in the context of epigenetics where patients with MDD exhibited increased levels of methylation on the BDNF promoter while treatments with antidepressant decreased BDNF promoter methylation [106]. Furthermore, it has been suggested that DNA methylation of BDNF in the peripheral blood can be used as a biomarker of epigenetic changes in the brain of patients susceptible to depression [107]. It is likely that these differential epigenetic responses in various brain regions may be responsible for the wide spectrum of symptoms observed in depressive patients.

Exposure to early life stress and subsequent epigenetic programming in the brain is hypothesised to be a potential cause of MDD later in life [108]. Postnatal adversity following maternal separation in rodents has been shown to lead to broad changes in histone modifying enzymes and to post-translational histone modifications. Rodents exposed to maternal separation display reduced levels of HDAC mRNA in the PFC [109], while some studies revealed elevated levels of histone acetylation [110, 111]. In addition, early life stress following maternal separation induces epigenetic changes in DNA methylation within the hypothalamus, a brain region associated with motivated behaviours [112]. Exposure to stressors prior to birth can also induce epigenetic changes potentially leading to the development of depression later in life. For example, significant differences in DNA methylation were observed in neonate umbilical cord blood sample taken from mothers suffering from depression and anxiety disorders [113]. Earlier studies had shown that early life experiences could have either beneficial or negative consequences to stress susceptibility in later life. For example, postnatal handling of young rodents decreased both stress reactivity and associated basal stress hormone levels in adulthood while maternal separation resulted in increased stress reactivity [114]. In addition to epigenetic changes associated with early life stress, there is growing literature suggesting that early life stress increases vulnerability in offsprings of these animals to stress [114, 115]. Furthermore transmission of susceptibility of stress and mood disorders has been observed in human subjects, where for example maternal, but not paternal, exposure to PTSD resulted in increased risk of PTSD in children of holocaust survivors [116]. Early animals studies of stress transmission had demonstrated that variation in maternal care served as a basis for a nongenomic behavioural transmission of individual differences in stress susceptibility across several generations [114, 115]. For instance when biological offsprings of mothers (dams) who exhibited low maternal caring behaviour were placed under the care of dams that exhibited high maternal caring behaviour, these offsprings exhibited significantly less fearful responses to novelty than the offsprings of dams who exhibited high maternal caring behaviour that had been subsequently placed under the care of dams exhibiting low maternal caring behaviour [114, 115]. Furthermore early life experience of maternal care was shown to induce differential expression of receptors associated with stress sensitivity, such as glucocorticoid, benzodiazepine and corticotropin-releasing factor (CRF) receptor mRNA [115]. A recent study had demonstrated transmission of stress vulnerability via epigenetic

mechanisms by changes in the germ cells that subsequently influence the behaviour of the offsprings for three generation in a gender dependent manner [117]. In addition to increased expression of the anxiety and depressive phenotype in mice that had undergone early life stress, epigenetic changes such as DNA methylation of several candidate genes associated with depression were found in the sperm germ line of these mice [117]. Strikingly, the study showed similar changes in DNA methylation in the brains of the female progeny that also exhibited both anxiety and depressive phenotypes [117]. These findings are extremely interesting as it demonstrates a potential mechanism by which stressful environmental factors can alter DNA methylation in the germline and that these alterations can be partly maintained across generations. The story, however, appears to be far more complex and subtle. In a study where mice had undergone CSD, offsprings, following natural breeding, of both stress-susceptible and stress-resilient mice were equally more vulnerable to stress [118]. Furthermore, male offsprings of fathers who had undergone CSD also exhibited significant disturbances in neuroendocrine signalling, specifically corticosterone and vestibular endothelial growth factor (VGEF), pathways previously shown to be associated with depressive-like phenotypes [119–121]. Since offsprings of males that had undergone CSD stress exposure were more vulnerable to stress in vitro fertilisation (IVF) experiments were performed in order to investigate whether the behavioural phenotype was directly transmissible through the sperm of the defeated mice. Sperm from defeated mice were used to impregnate normal female mice and the subsequent offsprings were put through a battery of behavioural measures of depression and anxiety. IVF derived mice from defeated fathers did not exhibit robust anxiety or depressive phenotypes on most measures except for the forced swim test paradigm [118]. With data from this study, together with observations that female rodents are able to adjust their reproductive investments depending on their interaction with the male, the authors concluded that the bulk of the vulnerabilities to stress are passed onto subsequent generations through behavioural mechanisms, possibly on the basis of the female detecting that she had procreated with an impaired male [118]. Given that FST alone was significantly different in IVF-derived mice [118] together with previous findings that epigenetic changes in DNA methylation was observed moderately in offsprings of stress vulnerable mice [117] could suggest that each gene possibly contributes to a small part of the behavioural phenotype and that these subtle differences were not robustly transmitted during IVF in the CSD paradigm.

In general, the evidence thus far suggests that global histone acetylation is pro-adaptive in response to stress and depression while aspects of histone methylation are pro-

depressant. Evidence linking early life stress with biological changes bridges the field of social and biological sciences and highlights the importance of developing a better social system for high-risk youths. Furthermore, advances in understanding epigenetic changes following stress exposure and possible mechanisms of transmission through the generations may lead to the potential development of specific tests to determine high-risk individuals and early treatment options.

Neurogenesis

The hypothesis that antidepressant medications might alleviate depression by increasing adult hippocampal neurogenesis [122] comes from observations that classical antidepressant therapy such as SSRIs take 3–4 weeks to have efficacy and that antidepressant treatment increases the numbers of adult-born neurons [123, 124], which take about 4 weeks to form synaptic connections [125]. Numerous chronic stressors such as repeated restraint stress, chronic unpredictable mild stress, social defeat stress, social isolation and corticosterone administration that induce depressive and anxiety-like behaviours all result in impaired adult hippocampal neurogenesis [126–130]. A recent study, however, did not find any evidence of hippocampal neurogenesis in mice following exposure to numerous stress-paradigms [131]. Since it is unclear in this study whether exposure to stressors induced depressive or anxiety-like behaviours in the mice (as they did not check for this), it has been hypothesised that chronic stress impairs hippocampal neurogenesis only in those animals that exhibit depressive or anxiety-like behaviours [132]. Hypersecretion and sustained elevations of the stress hormone cortisol is neurotoxic [133]. Furthermore, elevation of cortisol suppresses BDNF, which in turn leads to neurodegeneration and contributes to symptoms of depression [134]. The neurotropic factor BDNF is involved in neurogenesis by regulating neuronal differentiation and growth [135, 136]. Human post-mortem studies have shown decreased BDNF levels in the hippocampus of depressed patients [30]. It is likely that the decreased hippocampal volume in depressed patients may be associated with decreased BDNF levels [137–139]. Antidepressants in animals have been shown to reverse cortisol- or stress-induced suppression of cell proliferation [140–142]. In addition the SSRI sertraline was recently shown to increase neurogenesis in hippocampal progenitor cell lines by increasing protein kinase A signalling, glucocorticoid receptor phosphorylation and the subsequent activation of a specific subset of genes [143]. Regulation of glucocorticoid release following stress exposure serves numerous beneficial homeostatic functions while dysregulation of

glucocorticoids is associated with cognitive and depressive disorders [86, 144]. Within the hippocampus, a region abundant in glucocorticoid receptors that is also functionally important in cognitive and emotional behavioural processes, stress and elevated glucocorticoid levels inhibits neurogenesis [145]. Further evidence for the link between neurogenesis and stress come from recent findings that conditional inhibition of hippocampal neurogenesis, in a transgenic mouse line, lead to significant elevation of glucocorticoid levels following exposure to acute stress [146]. Furthermore, behavioural analysis on transgenic mice lacking the ability for neurogenesis found that these mice exhibited both baseline depressive phenotypes and greater susceptibility to stress when compared to wild-type controls [146]. Conversely, in experiments using an inducible transgenic mouse line in which adult neurogenesis could be increased demonstrated that these mice were resilient to chronic treatment with corticosterone, a mouse model of stress [147]. Neurogenesis may exhibit temporal characteristics in relation to depression. For example, immediately following exposure to CSD-stress, both stress-resilient and stress-susceptible mice exhibited increased levels of stress hormone and concomitant transient decrease in hippocampal neurogenesis that was normalised within 24 h [148]. Surprisingly, however, hippocampal neurogenesis was significantly elevated in stress-susceptible mice 4 weeks post-CSD [148]. Observations that ablation of hippocampal neurogenesis prior to CSD stress induced the stress-resilient phenotype strongly suggests that the compensatory enhancement of hippocampal neurogenesis is related to long-term individual differences in maladaptive stress responses [148]. The studies described above are interesting and point to a new avenue of research for treatments in mental disorder; however, the evidence for the role of neurogenesis and depression is still unclear. For example, neurogenesis does not occur in a significant amount in the elderly, yet antidepressants have been shown to be effective in treating elderly depressed patients [149]. Thus, although numerous studies have shown that stress decreases neurogenesis it should be noted that various studies have also reported no correlation between stress and neurogenesis [131]. For example, at the cellular level administration of antidepressant SSRIs have shown to 'demature' older granule cells to more plastics functional states without actually promoting neurogenesis [150, 151]. Furthermore, there are reports of antidepressants at behaviourally active or clinically relevant doses that do not exert any effect on processes involving neurogenesis [131]. Though, it should be noted that these analysis were performed on non-stressed, and presumably, non-depressed, animals. Other behavioural studies have highlighted a mixed bag of results. For example, one report, suggested inescapable shock decreased neurogenesis only after the development of contextual fear association, thus strongly suggesting that the important factor in modulation neurogenesis is not stress or fear, but the emotionally charged learning [152]. However, another study using a similar paradigm did not find any changes in neurogenesis even after the occurrence of substantial learning [153]. Another important complication in the findings is that the majority of the experiments in neurogenesis, and depression as a whole, are performed on males. Experiments utilising both males and females have found vastly different results between the sexes [154, 155]. Overall, the neurogenesis hypothesis of depression is supported by numerous studies; however, the existence of contradictory findings suggests that neurogenesis can be effected by stress and antidepressants under certain conditions but that these effects do not appear in all conditions of psychological stress, depression and antidepressant treatment [131]. It is clear that much more work is needed to clarify the role of neurogenesis and depression in different stress conditions and between the sexes.

Neural circuits

Deep brain stimulation (DBS) is a well-accepted procedure for the treatment of movement disorders such as Parkinson's disease [156]. Recent groundbreaking studies have shown that DBS, which involves delivery of focal electrical current to specific neural structures within the brain, rapidly alleviates symptoms of depression [9, 10]. The effectiveness of DBS in alleviating depression in patients when targeted to various brain regions suggests that depression is a neural circuit disorder [9, 157–161]. Figure 1 shows a representation of some of the regions of the brains and their connections that have been implicated in depression. DBS as a therapeutic option for treatment-resistant patients is based on the novel hypothesis that depression come about as a result of aberrations in communications between specific neural structures of the brain. Thus, focal neuromodulation with DBS is believed to 'reset' neural activity of aberrant circuits associated with depression. At present the mechanism by which the pathophysiology of neural circuits lead to depression is unclear. However, recent approaches combining animal models of depression together with electrophysiological, optogenetic and molecular analysis have begun to reveal a complex interplay between various neural circuits and cell types in encoding for depression [15, 162–168]. The mesolimbic dopaminergic pathway composed of dopaminergic (DA) neurons in the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc) is crucial for the recognition of emotionally salient stimuli such as reward [169] and aversion [170]. In addition DA neurons of the VTA-NAc circuit play
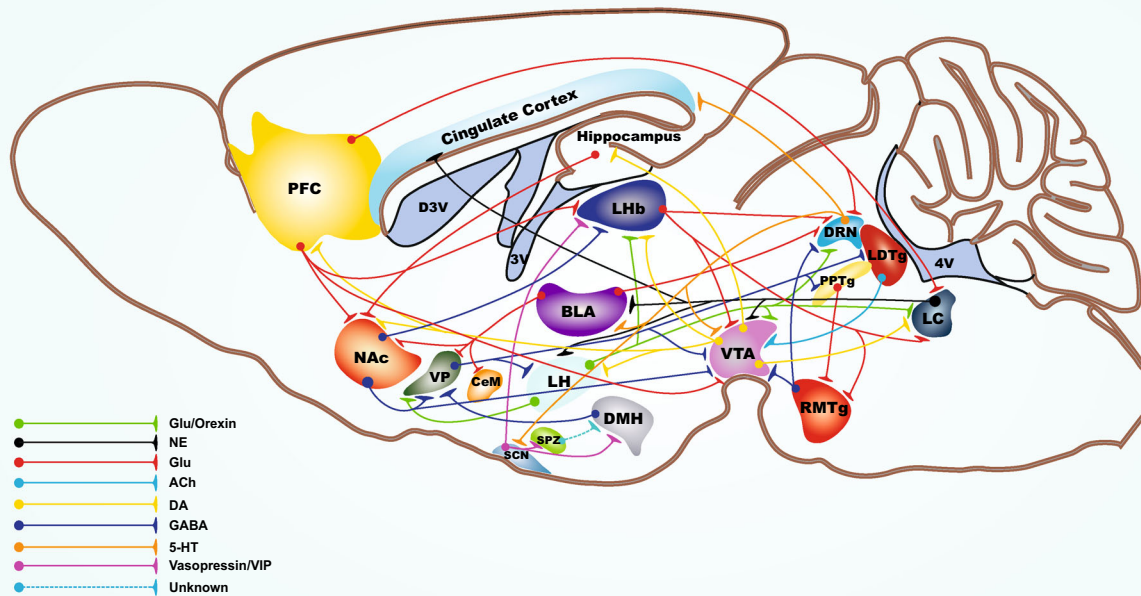
Fig. 1 Simplified schematic of the major neural circuit connections involved in encoding for depression-related behaviours. The network displays the complex interplay between numerous neurotransmitters in regulating cellular activity within various brain nuclei. *5-HT* serotonin, *ACh* acetylcholine, *DA* dopamine, *GABA* gamma-aminobutyric acid, *Glu* glutamate, *NE* norepinephrine, *VIP* vasoactive intestinal peptide

a key role in modulating depression-related behaviours [6, 12, 18, 20, 21, 163, 168, 171, 172]. Earlier work has shown that the in vitro firing rate and in vivo phasic firing events of VTA DA neurons in the brain's reward system is significantly increased in mice exhibiting the susceptible (depressed) phenotype following exposure to the chronic social defeat paradigm [12, 171, 173, 174]. Conversely in vivo recordings of rats susceptible to the learned helplessness paradigm exhibited decreased VTA DA neuron activity and that the antidepressant ketamine both rescued those rats previously susceptible to the learned helplessness paradigm and increased VTA DA activity [175]. Two recent optogenetic studies directly demonstrated the role of VTA DA neurons in depression [163, 168]. In one study optogenetic induction of phasic, but not tonic, firing of VTA DA neurons was shown to rapidly induce the susceptible (depressed) phenotype in mice that had previously undergone a subthreshold social defeat stress paradigm [163]. Conversely, the second study showed the opposite effects where phasic activity of VTA DA neurons rescued stress-induced depressive-like behaviour in mice that had undergone chronic mild stress [168]. The discrepancy between the two studies has been discussed [176, 177] and may highlight differential coding processes of VTA DA neurons for strong or weak stressful stimuli [166, 178], which is highly consistent with the fine context-detecting functions of VTA DA neurons [21]. It has recently been shown that rats put

through a strong stressful paradigm (restrained stress) exhibited increased firing in the VTA while those put through a weaker stress paradigm (mild inescapable stress) exhibited decreased activity [179]. A possible explanation for the differential coding for weak or strong stressors might lie in the existence of functionally distinct populations of VTA DA neurons. Those VTA DA neurons that exhibited decreased firing following weak stress exposure were located primarily in the medial and central portions of the VTA [179]. Furthermore, VTA DA neurons located in ventral VTA are excited by noxious footshock while dorsal VTA DA neural activity is inhibited [180]. Differential activity coding has also been demonstrated in mice exposed to the same stressor. VTA neurons projecting to the NAc (VTA-NAc) exhibit increased firing while those projecting to mPFC (VTA-mPFC) exhibit decreased firing in mice susceptible to social defeat stress [163]. Likewise, rapid induction of the depressed phenotype was observed by (1) optical induction of phasic activity in the VTA-NAc circuit and (2) optical inhibition of the VTA-mPFC circuit [163]. These projection-specific DA neurons exhibit differing physiological properties. DA neurons projecting to NAc exhibit robust I_h currents (hyperpolarisation-activated nonselective cation channel mediated currents) while DA neurons projecting to mPFC lack robust I_h currents [172, 181]. The degree of complexity of these circuits is evident by observations that subpopulations of VTA DA neurons

receive synaptic inputs from different nuclei in the brain. For example, neurons from the laterodorsal tegmentum (LDTg) synapses primarily on VTA DA neurons projecting to the NAc, while neurons from the lateral habenula (LHb) synapse either onto VTA DA neurons projecting to the mPFC or to GABAergic neurons in a portion of the VTA also known as the rostromedial tegmental nucleus—RMTg [182]. In addition, these circuits encode opposing behaviours where for example selective activation of LTD and LHb inputs to the VTA elicit reward and aversive behaviours respectively [182]. The LHb, a nucleus that integrates signalling from the basal frontal cortical areas and midbrain monoaminergic nuclei, has a functional role in motivated behaviours [183] and LHb neurons projecting specifically to the RMTg mediate behavioural avoidance [184]. Studies have shown increased activity of LHb neurons projecting to the VTA in mice exhibiting the depressed-phenotype following exposure to a learned helplessness model of depression [43] and to a chronic social defeat stress paradigm [185]. Furthermore, excitatory basal ganglia input to the LHb, that has been shown to encode aversive behaviour, is suppressed by serotonin [186]. This is interesting as it highlights a putative circuit that may be a target for classical monoaminergic uptake blocker antidepressants. The majority of neurons of the VTA are dopaminergic though a small percentage are glutamatergic and GABAergic [187]. The LHb is a key neuroanatomical regulator of midbrain reward circuits and increased activity of LHb projections to VTA is known to encode for depression [43, 185], it is likely, therefore, that aberration in the VTA-LHb-VTA loop may lead to depression-like behaviours. VTA DA neurons receive potent inhibitory inputs from the Ventral Pallidum (VP) while the basolateral amygdala, a region associated with stress and fear learning, sends excitatory glutamatergic inputs to the VP [188, 189]. As previously described in relation to stress, DA and depression, acute stressors activate the DA system [51] followed 24-h later by potent attenuation of DA activity [16]. A recent study had shown that the BLA-VP circuit mediates the decreased VTA DA neural activity in stress susceptible rats following exposure to CMS [190]. Evidence for the role of the BLA-VP-VTA circuit in modulating depression-related behaviours comes from the findings showing (a) the decreased VTA DA activity in CMS susceptible rats was restored by blockade of excitatory glutamatergic inputsto the VP, and (b) pharmacological activation of BLA decreases VTA DA activity [190].

Disregulation in signalling of the monoamine neurotransmitter, serotonin, in depression has been known for the last 60 years with the accidently discovery that inhibitors of monoamine neurotransmitter breakdown alleviate depression. The dorsal raphe nucleus (DRN), the main source of the brains serotonin (5-HT), is implicated in the pathophysiology and therapeutics of mental disorders such

as autism, anxiety and depression [191, 192]. The DRN has reciprocal projections with various regions of the brains involved in regulating emotions such as the LHb, hippocampus, hypothalamus, amygdala and cerebral cortex [191]. Furthermore, DRN, neurons are precisely regulated, both phasically and tonically, by glutamatergic and inhibitory GABAergic neural inputs from various regions implicated in mood disorders [193]. In line with the monoamine hypothesis of depression, 5-HT levels were decreased in mice exhibiting the depressed phenotype following chronic mild stress [194]. Furthermore, evidence suggests a close link between the LHb and DRN circuit in depression since lesion of the LHb alleviated symptoms of depression by increasing 5-HT levels [194]. The LHb and mPFC are critical regulators of DRN activity, where glutamatergic projections from these regions attenuate DRN activity via a feedforward inhibitory mechanism involving inhibitory interneurons [195–197]. Investigations into the micro-circuitry of DRN in encoding for depression showed increased excitability of GABAergic DRN neurons in mice susceptible, but not those resilient, to social defeat stress [198]. Furthermore, this study found associated decreases in 5-HT neuron activity in the DRN of susceptible, but not resilient mice, implicating that in the DRN, encoding for depression leads to increased GABA activity followed by the subsequent decrease in 5-HT neuron activity [198]. Follow-up studies showed a direct functional correlation between mPRC-DRN circuit activity and depression-related behaviours where optogenetic modulation of mPFC neurons projecting to DRN functionally increased DRN GABAergic interneuron activity and increased or decreased depressive-like behaviour in mice that undergone social defeat stress [197].

The locus coeruleus (LC), the major noradrenergic nuclei in the brain, is a vital component of the stress response. In rodents, stress increases LC activity [199] and treatments with antidepressants such as SSRIs, reduce LC activity, possibly via pre-synaptic autoreceptor activation [200]. Anatomically the LC has reciprocal connections with various regions of the brains also known to be associated with depression [201]. Significant increases in gene expression levels for NMDA and mGluR subunits were found in the LC of post-mortem depressed patients [16] supporting the notion that disrupted glutamatergic-noradrenergic interactions in the LC leads to depression. Electrophysiological measures of basal firing rates of LC neurons in the Wistar Kyoto (WKY) rat, a strain that exhibits baseline depressive and anxiety-like behaviours, was shown to be significantly higher compared to the standard Wistar strain of rats [202]. In addition LC neurons from the WKY were found to be less responsive to the inhibitory effect of Alpha2-adrenoreceptor activation [203]. Furthermore, a role for LC dysfunction in depression

comes from observations of robust glutamatergic projections from the PFC and LHb, two regions known to exhibit increased activity in depression [43, 44, 204, 205]. Neural processing of fear learning has recently been shown to pass from the lateral hypothalamus to the amygdala via the LC [206]. This study demonstrated that orexin (hypocretin) fibres from the lateral hypothalamus directly depolarize LC neurons via rapid co-release of glutamate and orexin leading to activation of NMDA and orexin-1 receptors, respectively. Furthermore, orexin activation of LC neurons leads to increased noradrenergic signalling, via beta adrenergic receptor in the lateral nucleus of the amygdala resulting in enhanced fear memory formation. Disregulation of this LH (orexinergic)-LC (noradrenergic)-amygdala circuit may be another possible mechanism by which depression occurs. Recently two populations of projection-specific neurons were identified in the basolateral amygdala that encode for reward and aversion [207]. The authors demonstrate that basal lateral amygdala (BLA) neurons projecting to the NAc exhibit increased synaptic plasticity in mice following reward training while BLA neurons projecting to the central amygdala (CeM) exhibited increased synaptic plasticity in mice that had undergone fear conditioning [207]. This finding further extends the notions that distinct population of neurons exists within a nuclei encoding for opposing behavioural phenotypes, and that aberration in balance between neural circuits may lead to mental disorders such as depression. Exposure to stress has shown shifts in the balance of network inputs from cortical and thalamic regions to the BLA. For example, activation of NE beta receptors following fear conditioned learning shifts the responses of LA neurons more robustly to the faster acting thalamic input over the slower cortical inputs [208]. The BLA receives inputs from the auditory thalamus and auditory association cortex where thalamic input encodes sensory information of the conditioned stimulus while the cortical pathway provides a more processed representation of the stimulus [209]. A recent neural circuit study extended the putative mechanistic role of DA regulation of networks within the BLA following exposure to stress. Specifically D2 receptor activation exhibited stronger net excitatory modulation of the auditory pathway and a stronger net inhibitory modulation of the cortical pathway [210]. The study of NE Beta and DA receptor modulation [208, 210] showing shifts in input towards subcortical pathways is believed to be an evolutionary advantageous fight-or-flight response in animals during acute stress while the slower cortical inputs is involved in evaluating complex environmental stimulus [208, 209]. Thus in relation to the two dynamically different processing pathways, it is hypothesised that chronic stress induces maladaptive changes in the brain [86] where, for example, repeated chronic stress could induce shifts in stronger

inputs from cortical inputs where organisms become more ruminative instead of proactive, as is proposed to occur in depression [211].

Increasing evidence shows that the NAc, a region typically associated with reward-related behaviours, has a critical role in depression symptomatology including reduced motivation and anhedonia [12, 14, 15, 20, 212, 213]. Medium spiny neurons (MSNs) of the NAc and dorsal striatum are enriched in D1 or D2 receptors and they send distinct projections to basal ganglia and reward structures. NAc D1-MSNs send projections to ventral pallidum, globus pallidum, VTA and substantia nigra (SN), while NAc D2-MSNs send projections to ventral pallidum [214, 215]. These two neural populations work in concert to promote normal behaviour while imbalance in one sub-type can promote dysfunctional motivational states [216–219]. The network balance model demonstrates that activation of D1-MSNs leads to positive reward behaviour while activation of D2-MSNs leads to aversive behaviours [217, 220–222]. Exposure to chronic social defeat was shown to differentially induce expression of the transcription factor delta FosB in the NAc MSNs. Mice susceptible to CSD stress expressed elevation of delta FosB in D2-MSNs while those resilient to CSD stress expressed elevation of delta FosB in D1-MSNs [223]. Furthermore, anhedonia following restrained stress is mediated by decreased excitatory synaptic strength of NAc D1-, but not D2-MSNs [224]. These findings were further extended in a recent study where mice susceptible to CSD exhibited decreased excitatory synaptic inputs into D1, but not D2-MSNs and that chronic chemogenetic attenuation of D1-MSNs, but not D2-MSNs, activity induced depressive-like behaviours in mice previously resilient to CSD stress [164]. Furthermore, repeated optogenetic activation of D2-MSNs induced depressive-like behaviour in mice exposed to a subthreshold social defeat paradigm [164]. These findings are exciting as it demonstrates: (a) two distinct circuit mechanisms within the NAc encode for depressive-like behaviours; and (b) changes in synaptic signalling in the NAC MSNs circuit most likely requires long-term molecular changes in order for the expression of depression-like behaviours since chronic, but not acute, optogenetic and chemogenetic manipulations were required to induce susceptibility to stress. Analysis of immediate early gene expression as a measure of neural activity found that expression levels of *Egr1* was decreased in the ventral hippocampus (vHIP) of mice resilient to CSD stress while *Arc* expression was decreased in mice susceptible to CSD [225]. Furthermore, physiological measures showed differential circuit specific synaptic adaptations following CSD where, in resilient mice, vHIP afferents projecting to NAc exhibited decreased glutamate release while mPFC afferents projecting to NAc exhibited increased glutamate

release [225]. The transcription factor delta FosB regulates transcription of numerous genes in the NAc [226, 227]. Two target genes of delta FosB, AMPA glutamate receptor subunit GluR2 and Sparc-like 1 (SC1) are upregulated in the NAc of mice resilient to CSD stress [212]. Furthermore, CHIPsec analysis showed significant binding of delta FosB on the GluR2 promoter and qPCR analysis revealed sustained GluR2 mRNA in NAc of resilient mice [212]. GluR2 subunit has profound effects on AMPA receptor function, where GluR2-lacking AMPA receptors are Ca^{2+}-permeable and show greater receptor conductance and strong inward rectification, as compared to GluR2-containing receptors [228]. This switch to GluR2-lacking AMPA receptors increases neuronal excitability [229]. Electrophysiological measure showed decrease in GluR2-mediated currents and increased inward rectification in stress susceptible, but not stress resilient mice, further implicating that increased excitability, in a subset of NAc neurons, encodes for depressive-like behaviour [212]. Several brain regions that mediate aspects of motivated, goal-directed, behaviours such as the ventral subiculum of the hippocampus, amygdala and prefrontal cortex send overlapping projections to the NAc where these inputs are integrated under dopaminergic modulatory control [230]. Furthermore, systems-level analysis has shown that DA receptor subtypes differentially regulate inputs to the NAc from the limbic system and PFC, where for example, tonic D2 receptor activation selectively attenuated inputs from the mPFC while phasic DA activity increases NAc neurons responsiveness to limbic inputs via activation of D1 receptors [231–234]. Aberration in the balance between these various inputs to the NAc is hypothesised to lead to the pathophysiology of motivated behaviours such as addiction and depression. A recent study using in vivo electrophysiology recordings in rats that had previously undergone a learned helplessness, depression, paradigm found decreased synaptic input from the vSub into the NAc of rats susceptible to, but not those resilient, to the depressive phenotype [175]. Furthermore, administration of the novel antidepressant ketamine both rescued the depressed phenotype in rats previously susceptible to the learned helplessness paradigm and also increased the vSub synaptic input to the NAc in these rats [175]. At the microcircuit level, decreased synaptic activity of vSub projections to the NAc shell, but not NAc core, specifically induced the depressed phenotype [175].

Dendritic spine plasticity is a critical element of experience-dependent reorganisation of the brain circuits and that maladaptive changes in dendritic spine development are suggested to underlie neuropsychiatric disorders such as depression, anxiety and addiction [6, 235–238]. Various stress paradigms lead to significant alterations in neuronal morphology in different cell types [239–241]. Furthermore,

BDNF and its downstream targets such as I_{KB} kinase (IKK) and the transcription factor nuclear factor kB (NF_{kB}) have been shown to be important regulators of neuronal structure [242, 243]. Mice susceptible to CSD stress exhibit dendritic remodelling (increased stubby spine formation) together with increased excitatory input into MSNs [14]. Furthermore, molecular analysis found increases in both IKK and the associated phosphorylated IkB proteins in the NAC of mice susceptible to social stress [14]. Evidence linking stress regulated changes in spine morphology and activation of IKK activity comes from approaches involving conditional knock down of IKK. Viral mediated conditional knock down of IKK by expression of IKK dominant negative (IKKdn) protein reversed the formation of stubby spines in mice susceptible to CSD stress [14]. Experience-dependent plasticity and the associated increases in synaptic input are known to lead to changes in spine morphology [236]. The observations that VTA DA neurons projecting to NAc exhibit increased phasic firing in stress susceptible mice [163] and that, the corticotropin stress hormone gates BDNF signalling in NAc MSNs [21], provides a mechanism by which increased BDNF induces changes in IKK enzyme activity leading to associated changes in dendritic spine morphology in the NAc of stress susceptible mice [14].

Homeostatic adaptations

Recent advances have highlighted possible mechanisms that determine the brain's ability to cope with stress. Multiple lines of evidence implicate dysregulation in the brain's reward circuit in depression [12, 20, 163, 168, 244]. Increased activity of VTA DA neurons has been causally linked to depression-related behaviours [12, 163, 171]. Increased activity of VTA DA neuron, in stress susceptible mice, is intrinsically induced by up-regulation of I_h, an excitatory driving force of VTA DA neurons [171, 245, 246] while pharmacological reduction of increased I_h in susceptible mice reverses depression [171]. Furthermore chronic antidepressant treatment with fluoxetine normalizes this hyperexcitability and decreases I_h in these neurons [171]. Together, these observations suggest that VTA DA neuron hyperactivity and increased excitatory I_h are both pathophysiological adaptations in mice susceptible to stress. A recent study confirmed that upregulation of I_h current in VTA DA neurons induced increased activity in these neurons in stress susceptible mice [172]. Surprisingly, while in resilient mice activity of these neurons was found to be normal, I_h current was even higher, which was observed in parallel with increased potassium (K^+) current [172]. The role of I_h current on mediating the resilient phenotype was determined by overexpression of the I_h

current related HCN channels in VTA DA neurons in susceptible mice. Here overexpression of HCN2 channel, thus further increasing I_h current in previously susceptible mice, induced the resilient phenotype [172]. In primary neuronal cultures, excessive hyperactivity has been shown to induce homeostatic upregulation of inhibitory driving force K^+-mediated current [247]. Repeated optogenetic activation of VTA DA neurons in susceptible mice, that presumably exhibit increased activity in these cells, was shown to induce the resilient phenotype together with associated decreased spontaneous activity and increased K^+-currents in these cells [172]. Furthermore, these observations were observed specifically in VTA DA neurons projecting to NAc but not mPFC, which correlates with previous projecting specific roles in encoding for depression [163]. Homeostatic plasticity plays a fundamental role in stabilising neuronal activity in response to excessive perturbations under both physiological [248, 249] and disease [250] conditions. Previous molecular analysis had shown that mice resilient to CSD stress exhibited normalised firing activity in VTA DA neurons associated with a corresponding increase in genes coding for subtype of K^+ channels [12]. Observations that VTA DA neurons of resilient mice exhibit upregulation of the excitatory driving force I_h and inhibitory driving force K^+-current suggests homeostatic plasticity plays a fundamental role in stabilising neural activity in promoting natural resilience to stress. Further investigations into homeostatic adaptive mechanisms leading to natural resilience have potential implication in the development of more naturalistic treatment strategies for mental disorders such as depression.

Immune response

Accumulating evidence suggests that inflammatory processes play a key role in the pathophysiology of depression [251, 252]. Post-mortem samples from patients with a history of depression express elevated levels of pro-inflammatory cytokines in the frontal cortex [253]. Rodents exposed to chronic mild stress exhibit neuroinflammatory markers [254] while administration of cytokine or lipopolysaccharide (a cytokine inducer) induced depressive-like behaviour [255, 256]. Extracellular signal regulated kinase (ERK1/2) is one of several mitogen-activated protein kinases (MAPK) involved in numerous cellular processes including long-term neural plasticity, cell maintenance, survival and immune responses [257–259]. ERK1/2 is also implicated in adaptive responses to stress and antidepressant treatment [260–262]. Acute and chronic exposure to chronic unpredictable stress increases phosphorylation of ERK1/2 and of two downstream targets

(ribosomal S6 kinase and mitogen- and stress-activated protein kinase 1) within the VTA [263]. In addition, pro-inflammatory cytokines modulate various MAPK including ERK [264]. Though depression and anxiety have been linked to depression, it is not clear if inflammatory status predates disease onset or whether it is a consequence of mood disorders. Recent studies, however, suggest that inflammatory status predates mental disease. Elevated levels of peripheral cytokines, in particular, interleukin-6 (IL-6), were found to be a good predicator of susceptibility to stress in mice exposed to both physical and purely emotional stressors [265]. Furthermore, bone marrow hematopoietic cell transplants from the susceptible donor mice to a stress naïve mice induced stress-susceptibility in the naïve mice when exposed to both physical and emotional stressors [265]. The observation that replacing the peripheral immune system of a stress-naïve animal with that of a stressed animal increases susceptibility to stressors suggests that the immune status of an animal with markers such as IL-6 can be used a predicator of susceptibility to stress. Conversely, findings that transgenic mice lacking IL-6 (IL-6$^{-/-}$) are resilient to stress suggest another potential strategy for the treatment of mood disorders [265]. Though it is intuitive to link inflammatory processes following stress/physical injury with depression, the data is still unclear. For example, a recent study in rodents and humans found that administration of anti-inflammatory drugs following electrode implantation attenuated the antidepressive effects of deep brain stimulation [266]. Future animal studies investigating the effect of manipulating molecular pathways involved in the immune response on animal models of depression together with human studies on immune-compromised patients with depression should help clarify this interesting field of study.

Circadian/sleep rhythm and depression

Though it has been known since the 1950s that daily rhythms are disrupted in patients suffering from MDD [267, 268], the molecular mechanisms linking aberration in circadian/sleep rhythms and mood disorders is still not well understood. In healthy humans, mood and reward are modulated by circadian phase [269, 270]. Mood disorders involve deficits in reward processing and motivation where perception in reward is blunted with a corresponding reduction in motivation to pursue hedonic goals. Circadian oscillation of gene expression, neural firing, neurotransmitter levels and receptor expression have been discovered in various brain regions implicated in mood-regulation and reward of both rodents and humans [271]. The Social Zeitgeber theory of mood disorders proposes that stressful

life events changes sleep/wake schedule that alters molecular and cellular rhythms in vulnerable individuals, leading to mood disorders [272]. In light of the close interaction between the circadian and sleep/wake rhythms, it is, therefore, not surprising that sleep deprivation therapy (SDT) rapidly alleviates depressive symptoms [273]. Studies over several decades have confirmed that SDT rapidly (within 24-h) reduces depressive symptoms in 40–60 % of patients [268, 274–276]. However, the drawback with SDT is that the majority of patients report relapses of depressive symptoms after the first bout of sleep [277, 278]. Though not yet determined, it is thought that SDT resets the aberrant circadian clock in depressive patients resulting in alleviation of symptoms [277, 278]. Accumulating clinical evidence highlights potential changes in circadian clock gene expression in depressed patients. Molecular analysis of clock genes in suicide vs non-suicides in postmortem found significant down regulation of *per1* in suicide victims [279]. Furthermore, microarray analysis of circadian clock gene expression in brain postmortem tissue taken from control and MDD human subjects found robust sinusoidal 24-h rhythms in control but not in MDD patients [280]. Mice susceptible to social defeat stress exhibit, fragmentation in sleep patterns and anxiety [281]. Expression of circadian gene *mper1* and *mper2* was decreased in the NAc of mice that exhibited increased anxiety-like behaviour [282]. Furthermore, viral knock down of *mper1/2* gene alone induced anxiety-like behaviour in mice, suggesting a causal link between aberration of circadian clock gene expression and anxiety/depression. Stress exposed mice also exhibited flattened diurnal locomotor activity returning to normal rhythms 7 days post-termination of stress [283]. Social defeat in the middle of the light phase increased both NREM sleep intensity and duration and decreased REM sleep [284]. Though limited in numbers, the few of studies of sleep deprivation (SD) on depression/anxiety have been promising. SD has been shown to reverse CSD stress-induced anxiety [285] and induce phase shifts in circadian clock gene expression [286, 287]. Molecular analyses of clock gene expression in mice following SD found elevated *Per1* and *Per2* levels in cortex, basal forebrain and hypothalamus which returned to normal levels following sleep recovery [288, 289]. Furthermore, SD has been shown to alter A) DNA binding of specific clock proteins BMAL, CLOCK and NPAS2 [290] and B) expression of various proteins known to be associated with depression such as GSK-3β, AMPA, Glutamate and mTOR [278]. Furthermore the rapidly acting antidepressant ketamine alters circadian gene expression [291], intracellular signalling molecule and neurotransmitter levels [278] and decreases aspects of REM sleep [292]. As mentioned previously, VTA DA neurons play a key role in modulating depression-related behaviours [12, 163, 171, 172] and it is likely that aberration in clock gene expression in the VTA may play a role in depression-related behaviours. Manipulation of *Clock* gene expression in the VTA modulates circadian rhythms, VTA neural activity and the depressive phenotype [293]. A more recent study extended the role of *Clock* gene and the regulation of anxiety related behaviours. *Clock* mutant mice were found to exhibit rapid mood cycling across the light–dark cycle such that the *Clock* mutants exhibited robust manic-like behaviour compared to wild-type controls when tested in an open field-, forced swim- and sucrose-preference test during the day [294]. Furthermore *Clock* mutant mice exhibited robust increases in both daytime tyrosine hydroxylase expression and VTA DA neuron activity [294]. Moreover, further evidence that the molecular components of the circadian timing system have a critical role in mood regulation comes from numerous findings that mutations of clock genes *Bmal1* and *Per2* induce mania-like behaviours in mice while knock-out of *Cryptochrome 1* and *2* genes induces altered anxiety-like behaviours [295–297]. The circadian nuclear receptor REV-ERBα, an important constituent of molecular circadian signalling that serves as transcriptional repressors of the *Bmal* RNA, has recently been shown to negatively regulate midbrain DA neuronal function via circadian modulation of tyrosine hydroxylase mRNA transcription [298]. REV-ERBα knockout mice exhibit altered circadian rhythmicity in mood related behaviours while conditional inhibition of REV-ERBα produces mania-like behaviour [298]. These recent findings further identify molecular connections between the circadian timing system and mood regulation that may potentially help specific targeting in the treatment of circadian-related mood disorders. Social interaction, a rewarding phenomenon in social animals such as mice, follows circadian rhythmicity [299] and since depression-like behaviour leads to aberration in neural processing in the reward system, it is likely that aberration in the circadian system results in aberration in reward processing in the reward centre leading to depression-related behaviours. Understanding the mechanism by which the circadian and sleep wake centres regulate depressive behaviours has great potential for the development of rapidly acting therapies for depression.

Conclusion

Depression is a complex mental illness where patients can express vastly different symptoms. It is evident from the literature reviewed above that the multiplicity of symptoms related to depression most likely is the result of aberrations in different aspects of normal neural functions that can

range from the molecular up to the neural circuit. The observation that classical antidepressant medications only work on a subset of patients indicates that depressive patients express aberration in different neural processes. Thus, to develop more effective and faster acting treatments for depression much work is still needed in understanding how exposure to stress lead to the sequence of changes in molecular, genetic/epigenetic processes and eventually neural circuit signalling. With the development of novel technologies to study molecular and genetic changes together with more sophisticated neural circuit analysis, it will be possible to better understand complex changes in the brain that ultimately lead to depression.

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