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REVIEW ARTICLE

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Hypothalamic corticotrophin releasing hormone neurons in stress-induced psychopathology: Revaluation of synaptic contributions

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Abstract

Stress has a strong influence on mental health around the world. Decades of research has sought to identify mechanisms through which stress contributes to psychiatric disorders such as depression, to potentially guide the development of therapeutics targeting stress systems. The hypothalamic pituitary adrenal (HPA) axis is the key endocrine system that is responsible for coordinating body-wide changes that are necessary for survival under stress, and much of the research aimed at understanding the mechanisms by which stress contributes to depression has focussed on HPA axis dysfunction. Corticotrophin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) sit at the apex of the HPA axis, integrating signals relevant to stress and external threats, to ensure HPA axis activity is appropriate for the given context. In addition to this, emerging research has demonstrated that neural activity in PVN^{CRH} neurons regulates stress related behaviours via modulation of downstream synaptic targets. This review will summarize convergent evidence from preclinical studies on chronic stress and clinical research in mood disorders demonstrating changes in PVN^{CRH} neural function, consider how this may influence synaptic targets of PVN^{CRH} neurons, and discuss the potential role of these PVN^{CRH} synaptic pathways in the development of maladaptive behaviours following chronic stress that are relevant to depression. We will also highlight important questions for future research aimed at precisely dissecting endocrine and synaptic roles of PVN^{CRH} neurons in chronic stress, their potential interactions, and therapeutic opportunities for the treatment of stress related disorders.

KEYWORDS
corticotrophin releasing hormone, depression, hypothalamus, stress

1 | STRESS RESPONSE SYSTEM

The stress response is an important system that coordinates behavioural and physiological adaptations necessary for overcoming real or perceived dangers, including shifts in behaviour, energy mobilization

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and immune function. While the dangers or threats experienced by modern humans may differ from those experienced by an animal in the wild, the stress response system continues to play an important adaptive role in our lives. However, despite this beneficial role, prolonged and excessive stress is an important risk factor for a diverse range of health conditions, including increased risk of mood and anxiety disorders such as depression. Better insight into how maladaptive stress impacts brain functions that underly behavioural disturbances in depression is important for understanding disease pathophysiology and guiding the development of targeted and more effective treatments.

Stress initiates a coordinated body-wide response via physiological and behavioural changes, in part through activation of the neuroendocrine stress pathway, the hypothalamic pituitary adrenal (HPA) axis. The final output of the HPA axis is release of the stress hormone cortisol (or corticosterone [CORT] in rodents), which acts on glucocorticoid receptors (GR) distributed around the body and brain, to elicit a synchronised shift in behaviour and physiology to support survival in the face of threats. The HPA axis is initiated by activation of corticotrophin-releasing hormone (CRH) neurons of the paraventricular nucleus of the hypothalamus (PVN), which in turn release CRH into the median eminence to act on the anterior pituitary. CRH stimulates adrenocorticotropin (ACTH) release from the anterior pituitary, which travels via the circulation to the adrenal cortex to promote the release of the glucocorticoid cortisol.[1] The CRH neurons in the PVN (PVN^{CRH}) receive monosynaptic input from diverse brain regions, including limbic areas such as the medial amygdala, locus coeruleus (LC), parabrachial nucleus (PBN), ventral hippocampus, bed nucleus of the stria terminalis (BNST), periaqueductal grey (PAG) and numerous hypothalamic nuclei,[2,3] to rapidly signal potential threat and activate the HPA axis response. The HPA axis is also regulated by a negative feedback loop, with glucocorticoids having an inhibitory effect on the endocrine activity of PVN^{CRH} neurons and the anterior pituitary. This is an important mechanism to maintain adaptive stress responses, by preventing excessive overactivation of the HPA axis and returning the system to baseline following stress exposure, in order to maintain homeostasis. Disruption of this homeostatic negative feedback is thought to play an important role in maladaptive stress responses during prolonged stress that may contribute to risk for psychiatric disorders like depression.[4]

In addition to these neuroendocrine functions of PVN^{CRH} neurons that are mediated by their projections to the median eminence, there is growing interest in PVN^{CRH} synaptic projections to other areas of the brain.[5,6] The potential importance of PVN^{CRH} synaptic connections outside the median eminence was first proposed 35 years ago,[7] and yet the function of these efferent circuits has only been explored in detail in recent years.[8] This delay can be partially explained by the limited availability of methods until quite recently that facilitate the precise dissection of neural circuit function. Important techniques for delineating the existence of PVN^{CRH} synaptic projections and their function have included transgenic approaches for genetically targeting CRH neurons (e.g., CRH-cre mouse line), combined with methods including ex vivo electrophysiology, optogenetics, calcium imaging and monosynaptic synaptic tracing. A diverse range of putative downstream synaptic targets of PVN^{CRH} neurons have been identified using these approaches (Table 1), and the role of some of these distinct pathways in adaptive stress responses (and other functions of PVN^{CRH} neurons) is slowly beginning to emerge. Alongside this research, an equally important question that has gained less attention is understanding PVN^{CRH} output pathway changes during prolonged stress, and their potential involvement in behavioural dysfunction associated with stress-related psychiatric disorders. The current review will briefly summarize evidence supporting the involvement of stress and dysfunctional stress response systems in depression and PVN^{CRH} neuron changes following prolonged stress. Following this, the review will focus on the emerging literature on synaptic targets of PVN^{CRH} neurons and discuss how established changes in PVN^{CRH} neuron functioning during prolonged stress may impact these pathways and their associated behaviours to contribute to the pathophysiology of stress related disorders including depression.

2 | STRESS AND DEPRESSION: EFFECTS ON THE BRAIN AND BEHAVIOUR

Stressful life events are an important risk factor for a number of different psychiatric disorders including depression.[22–25] This relationship has been highlighted during the ongoing covid19 pandemic, with reports of increased prevalence of depression associated with reduced mobility, which is likely to create stress due to social isolation and restriction of normal activities (covid-mental disorders[26]). Depression is associated with a range of behavioural changes, including well recognized symptoms such as depressed mood, feelings of worthlessness and guilt, anhedonia, and suicidal ideation. In addition to this, other changes that are less specific to depression but nonetheless impactful to patients include altered appetite, weight, sleep, concentration, decision making, activity and energy levels.[27] Despite a long history of research into the links between stress and depression, the mechanisms through which stress contributes to specific behavioural disturbances remain unclear. There is significant heterogeneity between different patients and within patients across time in the presentation of depression symptoms,[28] which may hinder analyses aimed at linking specific stress measures to symptom severity. Further, different symptoms are likely to be influenced by stress to different degrees and through distinct neurobiological mechanisms.

Preclinical models of chronic stress support a causal role for stress in the development of depression related phenotypes,[29] with convergent effects of a range of chronic stress models such as social defeat stress (SDS), unpredictable chronic mild stress (UCMS), early life stress (ELS), repeated restraint stress, chronic glucocorticoid exposure and learned helplessness.[30–35] Despite clear differences in the stress procures used across these models, which aim to reflect the different types of stress that can influence risk of psychopathology, similar effects on depression-related phenotypes are typically observed, including emergence of anhedonia, behavioural despair and anxiety.

TABLE 1 Anatomical evidence for PVN^{CRH} efferent projection pathways.

	Anterograde tracing	Ex vivo electrophysiology	Retrograde tracer/dual label	Rabies/dual label with CRH
NAcC	[9]			
BNST	[9]			
Thalamus	[9]			
BLA and LA	[9]			
PAG	[9]			
Hypothalamus (unspecified)	[9]			
PVN		[10,11]		(*Project to CRFR1 neurons*)[10]
LH	[12]	[8](*Project to ORX/HCRT neurons*[12])	*Overlap with ME projections*[8]	(*Project to ORX/HCRT neurons*)[13,14]
ME	[9]		*Distinct from VTA projections*[15]; *overlap with LH projections*[8]	
VTA	[9]		[16,17]	
SN			[18]	
Habenular	[12]			
LC	[12]		*Distinct from ME projections*[15]	
NST	[12]	[19]		
Raphe	[12]			
GPe				[20]

Note: Anterograde tracing using synaptophysin GFP/hrGFP AAVs has been performed in CRH-cre mice. Synaptic connectivity using optogenetic assisted electrophysiology in CRH-cre mice has demonstrated monosynaptic connectivity with downstream targets. Retrograde tracer/dual labelling using retrograde dyes or viruses combined with immuno- or transgenic labelling of CRH neurons has demonstrated synaptic projection targets. Rabies/dual labelling used monosynaptic labelling from a genetically defined starter population combined with immunolabelling of CRH neurons.[21] Regions in bold show stronger evidence (electrophysiology or retrograde tracing), which are also included in Figure 1.
Abbreviations: BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CRFR1, corticotrophin releasing hormone receptor 1; CRH, corticotrophin releasing hormone; GPe, globus pallidus externa; HCRT, hypocretin; LA lateral amygdala; LC, locus coeruleus; LH, lateral hypothalamus; ME, median eminence; NAcC, nucleus accumbens core; NST, nucleus of the solitary tract; ORX, orexin; PAG, periaqueductal grey; PVN, paraventricular nucleus of the hypothalamus; VTA, ventral tegmental area; SN, substantia nigra.

This convergence highlights distinct features of stress that are important for inducing behavioural phenotypes relevant to depression, including lack of control over the stress (e.g., unavoidable stress[36]) and lack of predictability.[37,38] For example, in learned helplessness and restraint stress models, subjects lack control over the stressor, whereas the unpredictable nature of stressors in UCMS and parenting behaviour in ELS (e.g., limited bedding model[39]) appear to contribute to their detrimental effects. These findings mirror clinical studies highlighting the important role of these features of stress in depression risk.[40] Thus, preclinical models provide a valuable framework for precisely examining the mechanisms through which stress impacts depression-related behaviours.

Stress has diverse effects on brain functions that are thought to be relevant to depression symptoms, and which are reviewed extensively elsewhere.[41–43] For example, convergent findings from clinical imaging in depression and rodent models of chronic stress suggest that stress may contribute to neural changes in depression observed in regions including the hippocampus and prefrontal cortex (PFC[44–46]). Hippocampal and PFC disturbances are likely to be important for behavioural despair, emotional dysregulation and learning and memory impairments in depression, although other brain systems likely also contribute to these symptoms. The HPA axis is thought to play a central role in these hippocampal and PFC changes observed in depression and following chronic stress, with stress hormone exposure in preclinical models mimicking many effects of chronic stress on these neural systems and depression-related behaviours.[32,47] However, HPA axis targeted treatments have not proven to be effective in clinical trials thus far.[48,49] Therefore, questions remain as to the precise changes in HPA axis function that occur in people with depression, how these changes are related to symptoms, and whether alternative mechanisms are involved in mediating stress effects in the disorder that could represent new treatment targets.

3 | NEUROENDOCRINE STRESS SYSTEM IN DEPRESSION

The HPA axis has been extensively studied in depression, and despite varied findings across studies some clarity has begun to

emerge.[50] For a number of years, a clear understanding of HPA axis changes in depression and their role in symptom development has been difficult to achieve, due in large part to methodological inconsistencies, patient heterogeneity, and comorbid diagnoses.[51] HPA axis function can be assessed through measurement of CRH, ACTH and cortisol in a variety of samples, including blood plasma and cerebrospinal fluid (CSF),[52,53] or less invasive approaches such as saliva and hair cortisol levels.[54,55] These measures can be taken under basal conditions, following stress or following activation of HPA axis negative feedback with an exogenous glucocorticoid challenge (dexamethasone). Furthermore, saliva and plasma levels show normal circadian fluctuations that can also be assessed,[56,57] although this can confound group comparisons if not properly controlled for. This highlights numerous potential sources of variability between studies, including which HPA axis component is measured, what sample is assessed and when the sample is collected. Hair cortisol is emerging as a useful biomarker for chronic stress that is resistant to confounding factors such as circadian release patterns (e.g., the time of day of sample collection) and acute stress (e.g., related to entering a laboratory for sample collection).[55] However, these hair measures are unlikely to show close associations with current symptoms, as hair cortisol reflects cumulative HPA axis function over the preceding months.[58]

Although heterogeneity across studies remains an issue, meta-analyses provide evidence for HPA axis hyperactivity in depression. However, these studies also point to strong effects of comorbid diagnoses, inpatient status and time of day of sample collection amongst other factors.[51,59,60] Further, a recent large analysis of depression symptoms in the English Longitudinal Study of Ageing (a community/nonclinical sample of $n = 4761$) found an association between hair cortisol and self-reported "somatic" symptoms (e.g., amotivation, sleep disturbances and lethargy) but not "cognitive affective symptoms" (e.g., feeling depressed, lonely and sad).[61] Together these findings may point to specific symptoms and/or subgroups of patients that would benefit most from treatments aimed at restoring HPA axis function. There is also literature suggesting a powerful role of ELS on HPA axis function, which may account for some of the effects and heterogeneity observed in studies of stress in depression.[62–65] Specifically, a number of studies have shown that adults with a history of ELS show HPA axis disturbances regardless of depression status, and that patients with depression and ELS show HPA axis changes relative healthy controls and patients depression but without history of ELS.[66] Given that stress in adulthood is also associated with increased depression onset,[24] it is possible that HPA axis disturbances may help explain the relationship between ELS and depression, whereas other causal mechanisms may be more involved in the effect of later life stress on depression. Together, these findings suggest that important gaps remain in understanding how stress contributes to depression when focussing exclusively on the HPA axis.

4 | PVN^{CRH} CHANGES ASSOCIATED WITH CHRONIC STRESS

PVN^{CRH} neurons show substantial changes in functioning across chronic stress, and its unsurprising that their potential involvement in depression has focussed on their contribution to HPA axis hyperactivity. However, consideration of these PVN^{CRH} neuron changes in the context of their synaptic projections may provide new clues about their potential involvement in the development of depression phenotypes following stress. PVN^{CRH} neuron changes across chronic stress are reviewed extensively by Herman and Tasker,[67] highlighting the convergent effects of chronic stress exposure in preclinical models on PVN^{CRH} neurons that typically produce a net increase in neuroendocrine function. These changes include increased expression of both CRH and arginine vasopressin (AVP) mRNA, decreased GR expression that mediates HPA axis negative feedback, and evidence of chronic hyperactivation (increased Delta FosB expression).[68–70] Some of these observations mirror changes observed in patients with depression, including increased CRH and AVP expression[71] and impaired dexamethasone suppression demonstrating reduced efficacy of HPA axis negative feedback.[65] It is important to note that HPA axis hyperactivity is linked to chronic unpredictable stress more so than chronic predictable stress (which tends to cause HPA axis hypoactivity or habituation[72,73]). Consistent with this observation, predictable chronic stress tends to produce opposite changes in PVN^{CRH} neuroendocrine markers, including decreased CRH mRNA,[74] although more intense repeated stress procedures may be somewhat resistant to this habituation of CRH mRNA expression. Specifically, increased CRH mRNA was observed with 2-h daily restraint[75,76] whereas decreased expression was observed with 1-h daily restraint.[74] Nonetheless, these alterations in PVN^{CRH} neuroendocrine markers may contribute to HPA axis dysfunction following chronic stress, although adaptations at other levels of the HPA axis will also determine the final output in terms of glucocorticoid release at both baseline and following acute challenge.

In addition to these endocrine-related changes in PVN^{CRH} functioning following chronic stress, substantial changes in PVN^{CRH} neuronal excitability have been described, although this has received less attention in relation to mechanisms of stress-related psychiatric disorders. Increased excitability of PVN^{CRH} neurons following chronic stress has been shown to arise from multiple changes, including increased glutamatergic and noradrenergic terminal appositions[77] and increased excitatory synaptic inputs.[78] Parallel reduction of inhibition of PVN^{CRH} neurons is also observed, including reduced inhibitory inputs,[78,79] decreased expression of several $GABA_A$ receptor subunits[79] and rearrangement of inhibitory synapses including decreased soma inputs.[80] While these effects to enhance the excitability of PVN^{CRH} would be expected to contribute to altered endocrine output through activity dependent CRH release, it is also valuable to consider how these changes may impact activity of PVN^{CRH} synaptic projections throughout the brain, and how this may contribute to chronic stress effects on maladaptive behaviour.

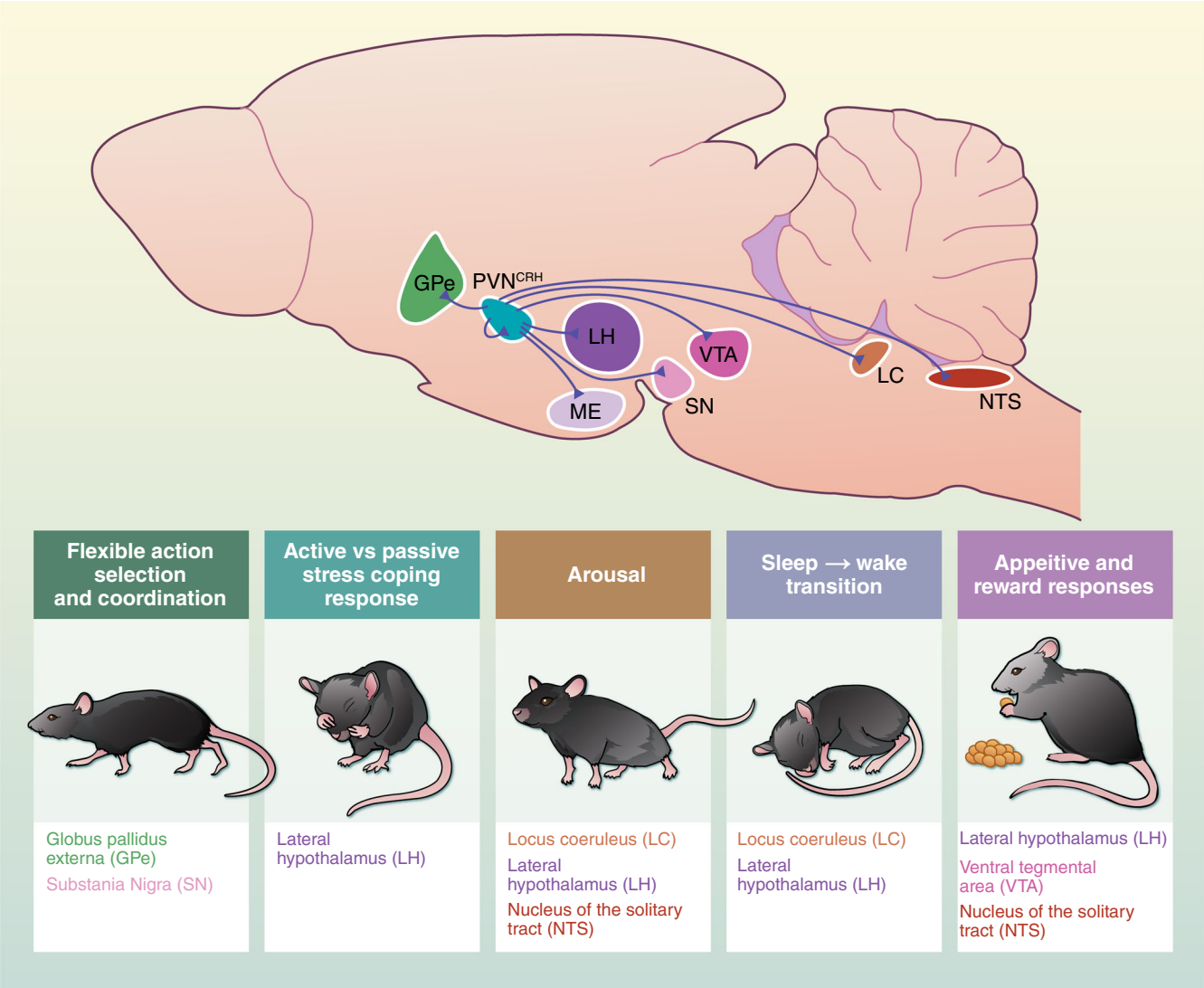

FIGURE 1 Overview of validated synaptic projection targets of PVN^{CRH} neurons. The top panel shows downstream targets of PVN^{CRH} neurons that have been validated by using retrograde tracing or electrophysiology. Further targets that have been proposed based on anterograde tracing are included in addition to these in Table 1. The bottom panel outlines several key behavioural domains that are associated with one or more of these synaptic targets of PVN^{CRH} neurons, although it is largely unknown how projections from PVN^{CRH} neurons may contribute to these functions. CRH, corticotrophin releasing hormone; GPe, globus pallidus externa; LC, locus coeruleus; LH, lateral hypothalamus; ME, median eminence; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus of the hypothalamus; SN, substantia nigra; VTA, ventral tegmental area.

When beginning to consider how chronic stress might impact activity in PVN^{CRH} synaptic pathways, it would be straight forward to assume that synaptic activity would change similarly to HPA axis function across chronic stress. However recent evidence suggests distinct control of PVN^{CRH} endocrine and synaptic functions, with acute CORT-mediated negative feedback having relatively little impact on the neural activity of PVN^{CRH} neurons in response to acute and repeated stressors.[81] Furthermore, there is emerging evidence that during prolonged glucocorticoid exposure (1 week), PVN^{CRH} neurons escape negative feedback pressure via neuroplastic changes, resulting in blunted CORT response to stress while PVN^{CRH} neural activity is maintained (preprint form[82]). In these studies, in vivo PVN^{CRH} recordings have been performed using bulk fibre photometry, which sums activity across all genetically identified PVN^{CRH} neurons under the optic fibre. While valuable, this approach does not differentiate between individual neurons, disregarding heterogeneity across the PVN^{CRH} population that may help clarify how chronic stress impacts PVN^{CRH} activity.[83] Specifically, different subpopulations of PVN^{CRH} neurons may show distinct activity profiles in response to chronic stress, that may reflect differential involvement in processes that are under negative feedback control (e.g., HPA axis) versus those that may not be (e.g., rapid defensive responses). Alternative methods will be necessary to address these questions, such as in vivo electrophysiology or calcium imaging with two-photon or miniature microscopes, to resolve the activity of individual PVN^{CRH} neurons. This will be an important consideration for future research investigating the impact

of chronic stress paradigms, that are associated with dampened negative feedback response and HPA axis hyperactivity, on the activity of PVN^{CRH} neurons and their synaptic projections.

5 | ANATOMICAL EVIDENCE FOR PVN^{CRH} PROJECTION PATHWAYS

Recent studies using optical recordings and manipulations in vivo have highlighted the fast timescales through which changes in PVN^{CRH} neural activity correspond with stress-related behaviours.[3,8,13,81,84,85] These timescales are incompatible with the slower actions of the HPA axis, suggesting important synaptic functions of this population that operate alongside and potentially independently of their neuroendocrine effects. Extrahypothalamic projections of PVN neurons have been investigated for decades,[86] and synaptic connections of the PVN^{CRH} subpopulation outside the median eminence were first proposed by Rho and Swanson.[7] At this time the breadth of downstream synaptic targets of PVN^{CRH} neurons was unclear, and this is continuing to emerge even today. A growing body of evidence has highlighted putative synaptic projections of PVN^{CRH} neurons throughout the brain that may contribute to rapid behavioural responses to stress (Table 1, Figure 1). In recent years, a variety of methods have been used to identify these PVN^{CRH} efferent pathways, including transgenic anterograde tracing, electrophysiology, and retrograde tracers including dyes (e.g., Fluorogold), adeno-associated viruses (AAVs) and monosynaptic rabies approaches, with many of these advances utilizing CRH-cre transgenic mouse lines.

The downstream target of PVN^{CRH} neurons that has received the most attention is the lateral hypothalamus (LH). The LH is an important regulator of motivation and arousal,[87] with orexin/hypocretin (ORX/HCRT) neurons playing a central role in these functions. Fuzesi et al. first demonstrated a synaptic connection between PVN^{CRH} neurons and the LH, and used optogenetics to demonstrate that activation of this pathway promoted self-grooming, which is a self-directed stress coping strategy.[8] This effect was similar to the increase in grooming observed following acute stress or optogenetic stimulation of PVN^{CRH} neuron cell bodies, and inhibition of PVN^{CRH} cell bodies during stress shifted post-stress behaviours away from coping/de-arousal and towards exploratory and hypervigilant behaviours.[8] These important findings demonstrated for the first time that synaptic projections of PVN^{CRH} neurons control rapid behavioural responses to stress that are separate to PVN^{CRH} neuroendocrine functions.

Given the important role of LH ORX/HCRT neurons in the control of sleep–wake cycles, other groups have investigated the involvement of the PVN^{CRH} input to the LH in this process. Optogenetic stimulation of PVN^{CRH}-LH circuit was found to induce wakefulness,[12,13] and this effect was dependent on normal CRH gene function in PVN^{CRH} neurons, which presumably reflects an important role of CRH release in the LH. It has recently been demonstrated that PVN^{CRH} neurons directly innervate ORX/HCRT neurons, using monosynaptic rabies tracing[13,14] and ex vivo electrophysiology,[12] and PVN^{CRH} inputs to ORX/HCRT neurons appear to partially mediate their effect on wakefulness.[13] More work is needed to understand whether other behaviours mediated by PVN^{CRH}-LH synaptic projections depend on direct inputs to ORX/HCRT neurons (e.g., grooming phenotype described by Fuzesi et al.[8]), whether other LH neuron subtypes are targeted by PVN^{CRH} neurons, and what the function of those connections might be. The LH also plays a central role in appetitive and motivated behaviour, with distinct contributions from subpopulations including ORX/HCRT neurons,[88] melanin-concentrating hormone (MCH) neurons[89] and GABA-ergic neurons.[90] Studies using genetically encoded activity indicators and fibre photometry have revealed that neural activity is suppressed in PVN^{CRH} neurons during reward investigation and consumption;[3,85] however, the role of PVN^{CRH}-LH projections in reward-related behaviours remains unexplored.

Less is known about the function of other synaptic targets of PVN^{CRH} neurons that have been identified using electrophysiology or retrograde tracing with dual labelling for CRH (Figure 1). Projections to regions within the basal ganglia circuitry have emerged as a key target of PVN^{CRH} synaptic connections, including the globus pallidus externa (GPe) of the indirect pathway,[20] the ventral tegmental area (VTA),[16,17] and more recent evidence for inputs to the substantia nigra (SN[18]). PVN^{CRH} projections to these targets may influence processes such as action selection and coordination, decision making and reward processing. Strong data also suggests that PVN^{CRH} neurons directly project to the LC, where central noradrenergic (NA) neurons are found,[15] and this pathway may compliment the role of projections to the LH in the regulation of arousal and sleep–wake cycles. PVN^{CRH} projections to the nucleus of the solitary tract (NTS) have also been identified using ex vivo electrophysiology, and functional interrogation using optogenetics has demonstrated that activation of this pathway increases blood pressure and heart rate, which could contribute to regulation of arousal.[19] The NTS is also involved in processing gustatory information, with important influences on appetitive and reward processing,[91,92] although it is unknown whether PVN^{CRH} neurons innervating the NTS populations are involved with these functions. Projections from PVN^{CRH} neurons onto other neurons within the PVN that express CRH receptor 1 (CRHR1) have also been identified.[10,11] These PVN^{CRHR1} neurons appear to be involved in maintenance of HPA axis responsivity across chronic stress,[11] although it is unclear whether or how inputs from PVN^{CRH} neurons contribute to these effects.

A wide range of other PVN^{CRH} targets throughout the brain have been proposed based on anterograde tracing data from two studies.[9,12] These include many limbic structures such as the BNST, the basolateral and lateral amygdala (BLA and LA), the habenular, thalamus and nucleus accumbens core (NAcC), and other important structures regulating mood and arousal including the raphe and PAG. However, it should be noted that the two PVN^{CRH} anterograde tracing studies failed to report overlapping targets, suggesting that validation with other methods such as retrograde tracing or electrophysiology is warranted. Nevertheless, these findings highlight the growing evidence for wide ranging synaptic targets of PVN^{CRH} neurons, that may play an important role in a variety of stress induced

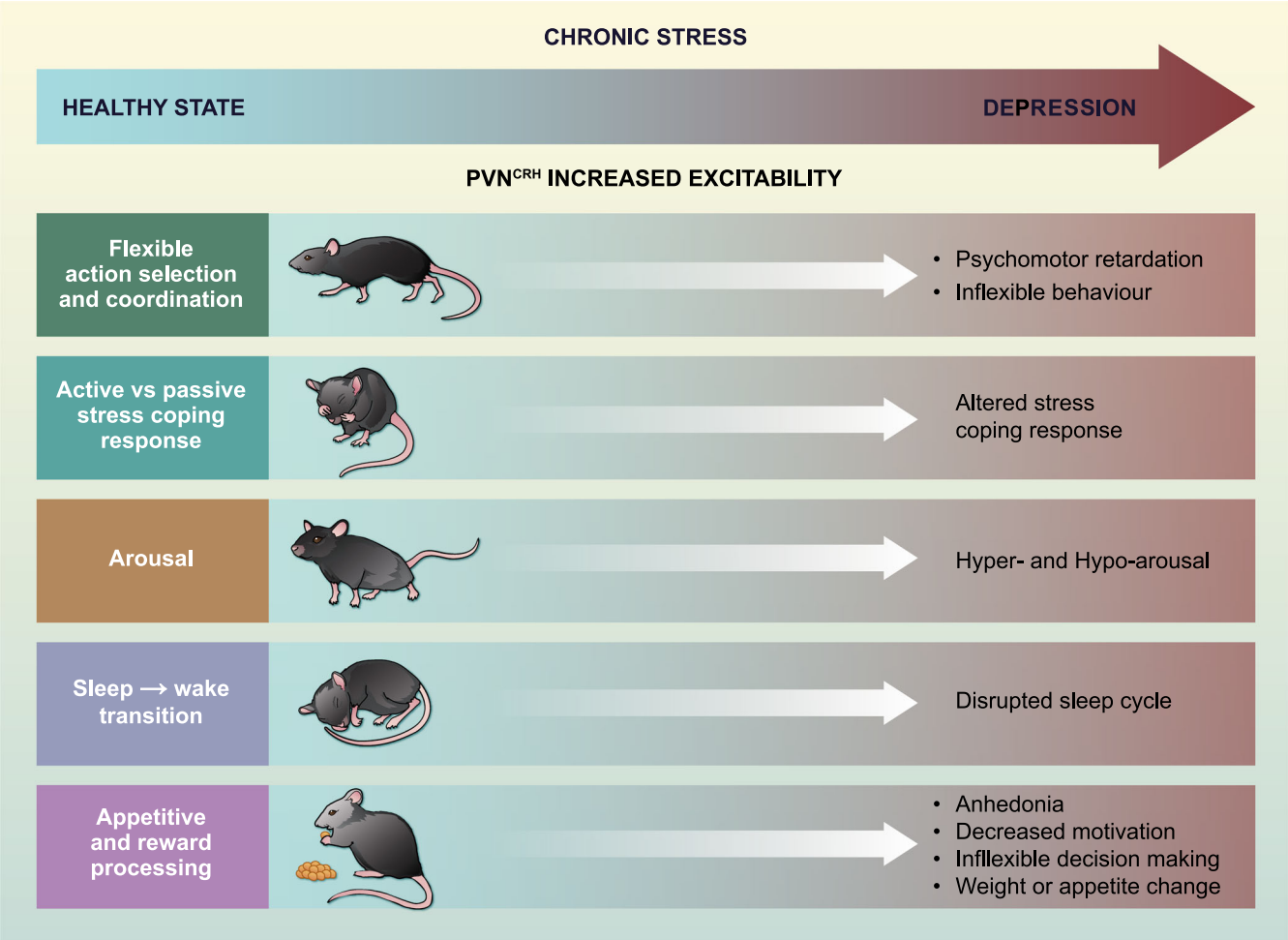

FIGURE 2 Framework for understanding how changes in PVN^{CRH} neuron function during chronic stress may contribute to development of depression phenotype via synaptic projections. Chronic stress is associated with increased risk for depression, and preclinical models have shown that PVN^{CRH} neurons show adaptations resulting in increased excitability across chronic stress exposure. We propose that these changes in PVN^{CRH} neuronal function are likely to alter synaptic activity in their efferent pathways, which may contribute to pathological changes in behaviour following chronic stress that are relevant to depression, based on the contribution of PVN^{CRH} downstream projection targets to relevant behaviour domains that were highlighted in Figure 1.

behavioural adaptations based on the diverse functions of these downstream target regions. Better understanding of the function of these circuits may assist revaluation of the role of PVN^{CRH} neurons in the stress response beyond their neuroendocrine functions, in both health and disease.

6 | A POTENTIAL ROLE FOR PVN^{CRH} PROJECTION PATHWAYS IN THE LINK BETWEEN STRESS AND DEPRESSION

These new findings about synaptic targets of PVN^{CRH} neurons may help to fill gaps in our understanding of how stress contributes to depression. Given that chronic stress increases both depression susceptibility and PVN^{CRH} neuron excitability, this raises the question of whether aberrant neural activity in PVN^{CRH} synaptic pathways during chronic stress is involved in the development of specific aspects of depression (Figure 2). Research to address this hypothesis can use functional analysis of these distinct efferent circuits using targeted transgenic approaches (e.g., optogenetics and optical recordings) combined with translational behavioural paradigms relevant to depression. Despite challenges in assessing some aspects of depression symptomatology that are unique to humans or difficult to verify in preclinical models, such as depressed mood, feelings of worthlessness and guilt, and suicidal ideation, there are other features of depression diagnostic criteria that are more readily measurable in preclinical rodent models.[93] These more translational features of depression include psychomotor retardation, inflexible decision making, disturbed sleep, weight changes and altered reward processing.

Interestingly, many of these translational features of depression are relevant to behavioural domains that may be regulated by PVN^{CRH} synaptic projections (Figure 2). For example, PVN^{CRH} neurons may impact arousal and sleep changes relevant to depression following chronic stress via aberrant activity in projections targeting the LH, LC

and/or NTS, which are critically involved in those processes. Furthermore, PVN^{CRH} circuits targeting the LH, VTA and/or NTS may be involved in anhedonia, altered reward learning or changes in weight related to altered appetitive drive following chronic stress exposure. Functional dissection of the PVN^{CRH}-LH pathway has provided some support for these hypotheses, with acute activation of PVN^{CRH}-LH circuit promoting insomnia[13] and acute inhibition of PVN^{CRH}-LH circuit shifting stress coping strategies,[8] which are relevant to behavioural changes observed in depression. However, whether these and other PVN^{CRH} efferent circuits contribute to pathological changes in behaviour relevant to depression that are associated with chronic stress is yet to be determined. Establishing whether causal relationships exist may help guide the development of novel therapeutics for depression targeting PVN^{CRH} neurons, with a new focus on their synaptic functions, rather than following the path of previous attempts to develop new treatments targeting their neuroendocrine functions.

Future studies should also prioritize analysis of potential sex differences in the role of synaptic pathways of PVN^{CRH} neurons in the development of depression phenotypes following chronic stress,[94] particularly given important sex differences in stress responses[95] and depression risk.[96] Much of the existing literature on PVN^{CRH} neural functioning and effects on chronic stress involves male subjects only (or sex is not reported), however the limited work examining sex differences has shown sex-specific plasticity of synaptic inputs onto PVN^{CRH} neurons following chronic stress[97] and sex-specific social buffering of acute stress induced synaptic dysfunction in PVN^{CRH} neurons.[98,99] These findings suggest a need for more research to understand potential sex differences in PVN^{CRH} neuron function across chronic stress, that may be particularly relevant in the context of depression.

7 | CONCLUSIONS

The goal of this review was to highlight how the recent characterization of synaptic projections of PVN^{CRH} neurons that operate alongside, and likely independent of, their role in the HPA axis, may inform a new understanding about the role of this population in disease states. Specifically, this new insight on PVN^{CRH} function highlights opportunities for investigating the role of these novel pathways in the development of depression related phenotypes following chronic stress. Importantly, this proposal does not dismiss or rule out the contribution of other brain pathways to chronic stress effects on behaviours and the symptoms of depression, nor that changes in HPA axis functioning may contribute to development of depression phenotypes following chronic stress, as extensive evidence supports these ides. Rather, by highlighting new avenues for research, it is hoped that this framework may help to fill gaps in our current understanding of how stress contributes to the development of depression. New mechanistic understanding of depression, based on synaptic projections of PVN^{CRH} neurons, can potentially inform the development of more effective depression treatments, and even prophylactic strategies that may prevent PVN^{CRH} synaptic disturbances contributing to symptoms. New research beyond the endocrine functions of PVN^{CRH} neurons in chronic stress and depression is necessary to evaluate these possibilities.

AUTHOR CONTRIBUTIONS

Laura M Stanton: Conceptualization; investigation; writing – original draft; writing – review and editing. **Aidan J Price:** Conceptualization; investigation; writing – original draft; writing – review and editing. **Elizabeth E Manning:** Conceptualization; funding acquisition; investigation; supervision; writing – original draft; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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