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Anteroventral bed nuclei of the stria terminalis neurocircuitry: Towards an integration of HPA axis modulation with coping behaviors - Curt Richter Award Paper 2017

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ABSTRACT

A network of interconnected cell groups in the limbic forebrain regulates hypothalamic-pituitary-adrenal (HPA) axis activation and behavioral responses to emotionally stressful experiences, and chronic disruption of these systems chronically is implicated in the pathogenesis of psychiatric illnesses. A significant challenge has been to unravel the circuitry and mechanisms providing for regulation of HPA activity, as these limbic forebrain regions do not provide any direct innervation of HPA effector cell groups in the paraventricular hypothalamus (PVH). Moreover, information regarding how endocrine and behavioral responses are integrated has remained obscure. Here we summarize work from our laboratory showing that anteroventral (av) bed nuclei of the stria terminalis (BST) acts as a point of convergence between the limbic forebrain and PVH, receiving and coordinating upstream influences, and restraining HPA axis output in response to inescapable stressors. Recent studies highlight a more expansive modulatory role for avBST as one that coordinates HPA-inhibitory influences while concurrently suppressing passive behavioral responses via divergent pathways. avBST is uniquely positioned to convey endocrine and behavioral alterations resulting from chronic stress exposure, such as HPA axis hyperactivity and increased passive coping strategies, that may result from synaptic reorganization in upstream limbic cortical regions. We discuss how these studies give new insights into understanding the systems-level organization of stress response circuitry, the neurobiology of coping styles, and BST circuit dysfunction in stress-related psychiatric disorders.

1. Introduction

Stress may be broadly defined as the constellation of physiological and behavioral responses to any challenge that overwhelms, or is perceived to overwhelm, selective homeostatic systems of the individual (Day, 2005; Selye, 1980). Integral to the stress response is the induction of neuroendocrine (hypothalamo–pituitary–adrenal or HPA) and autonomic (sympatho-adrenal) systems for the mobilization and redistribution of bodily resources to facilitate and complement situation-specific adaptations for the particular challenge at hand. Glucocorticoid end-products of the HPA axis (cortisol in humans, corticosterone in rodents) are potent hormonal mediators that act broadly, and over extended time periods, to help prepare the individual for emergency conditions. Recruitment of this response system facilitates coping with acute insults, but since prolonged glucocorticoid exposure can produce catabolic, immunosuppressive, and even neurotoxic effects, sustained or repeated stress exposure may be accompanied with significant health risks. This is true of one major class of experimental stress paradigms, termed emotional stresses, which are generally viewed as modeling the set of physiological and behavioral alterations that result from challenges encountered by humans in modern existence. The identity of, and degree to which, a given response may be engaged by emotionally stressful events requires an evaluative function to compare the current threat with past experience and/or the engagement of species-specific behavioral responses. Such appraisals, and their capacity to modulate stress responses, are the domain of an interconnected network of cerebral cortical and limbic regions of the telencephalon.

The past quarter century has seen a substantial degree of progress in unraveling the neural pathways and mechanisms accounting for how the limbic forebrain modulates the HPA axis response to emotional

Abbreviations: avBST, anteroventral subdivision of the bed nuclei of the stria terminalis; BST, bed nuclei of the stria terminalis; CRF, corticotropin-releasing factor; CVS, chronic variable stress; GAD, glutamic acid decarboxylase; GAD-65, glutamic acid decarboxylase, 65 kD isoform; HPA, hypothalamo-pituitary-adrenal; mPFC, medial prefrontal cortex; PAG, periaqueductal gray area; PL, prelimbic cortex; PVH, paraventricular nucleus of the hypothalamus; PVT, paraventricular nucleus of the thalamus; VGLUT2, vesicular glutamate transporter, type 2 isoform; vlPAG, ventrolateral subdivision of the periaqueductal gray area; vSUB, ventral subiculum; VTA, ventral tegmental area

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stressors. Emphasis on studying this particular aspect of the stress response is based on the far-reaching health consequences that come with HPA axis dysregulation and aberrant glucocorticoid secretion. Further insight into stress-related disease susceptibility will likely derive from elucidating the neural basis of individual variability in HPA axis reactivity, and how chronic challenges produce differential adaptations of HPA output (i.e., habituation, sensitization). Early work featured the hippocampus as the key modulator and target of stress-induced HPA activity and glucocorticoids, whereas subsequent studies highlight a broader interconnected array of limbic forebrain structures (e.g., prefrontal cortex, hippocampus, paraventricular nucleus of the thalamus) capable of providing HPA-inhibitory influences. That these influences are largely mediated via indirect, predominantly GABAergic relays, before converging onto HPA neurosecretory neurons in paraventricular nucleus of the hypothalamus (PVH), casts light onto a basic organizational principle governing top-down control of HPA effector systems.

Interestingly, the key elements of this limbic-HPA modulatory "network" are more often regarded in behavioral regulation as opposed to neuroendocrine functioning. That much of the past work investigating limbic forebrain involvement of HPA activity or behavior has been conducted in isolation from one another, has hampered our understanding of where these and other functions are integrated. Nevertheless, the examination of individual variability in stress reactivity and coping styles raises the possibility that nodal points exist for the coordination of behavioral with endocrine responses (de Boer et al., 2016). For example, reactive/passive behavioral response strategies have been widely associated with elevated HPA activity, however the neural mechanisms accounting for the coordination of these functions have remained elusive.

In this review, we will highlight recent findings from our laboratory that the anteroventral (av) bed nuclei of the stria terminalis (BST) acts as a neural hub for coordinating restraining influences on both the HPA axis and passive behavioral responses to inescapable challenges. The avBST itself resides within an anatomical network of cell groups commonly regarded as the central extended amygdala. This network is comprised of interconnected circuits involving the central nucleus of the amygdala and multiple subdivisions within the BST, that share common morphological and neurochemical characteristics and have been widely implicated in the processing fear- and anxiety-related information (Alheid and Heimer, 1988; Fox et al., 2015; Swanson and Petrovich, 1998; Walker et al., 2003a). Evidence will suggest that avBST's place in this network appears to be more important for coordinating neuroendocrine with behavioral responses than other components of the central extended amygdala. Moreover, avBST is uniquely positioned to convey differential adaptations resulting from chronic exposure to stress, such as HPA axis sensitization and increased passive behaviors, that result from synaptic reorganization in upstream limbic cortical regions, such as medial prefrontal cortex (mPFC) and hippocampus. We will discuss the implications of a pathway capable of integrating specific features of the stress response in terms of reactive coping styles and disease susceptibility. Whereas BST is involved in the coordination of anxiety-related autonomic and behavioral responses, we propose that much of these functions hail from more dorsal aspects of this structure. When considered in the context of the current discussion, we propose a regional differentiation for avBST involvement in more neuroendocrine-related psychiatric contexts than is currently regarded.

2. Limbic modulation of the HPA axis– a framework for understanding the central organization of stress modulatory systems

Evidence for avBST involvement as a coordinator of adaptive responses to stress were borne out of attempts to understand the central organization of HPA axis control during stress (Dayas et al., 2001; Herman et al., 2003; Radley, 2012; Sawchenko et al., 2000; Spencer et al., 2005; Ulrich-Lai and Herman, 2009; Van de Kar and Blair, 1999). Emotional stressors require interpretation by exteroceptive sensory systems, as well as integration with distinct cognitive and affective information processing systems in the brain (Dayas et al., 2001; Herman and Cullinan, 1997; Sawchenko et al., 2000). Whereas this class of stressors ultimately engage brainstem and hypothalamic effectors for activation of the sympatho-adrenal and HPA axis output, they also manifest widespread activation in the limbic forebrain, corresponding to a broad array of behavioral (e.g., vigilance, fear), physiological, and endocrine changes that help to facilitate adaptive coping as required by the particular environmental demand (Campeau and Watson, 1997; Dayas et al., 2001; Herman et al., 1995b; Li and Sawchenko, 1998). Past functional and lesion studies implicate a network of limbic forebrain circuitry in the inhibitory control of HPA activation during emotional stress (Akana et al., 2001; Christoffel et al., 2011; Cullinan et al., 1995; Herman and Cullinan, 1997; Jaferi and Bhatnagar, 2006). While the amygdaloid complex, hippocampal formation and mPFC are prominent in HPA axis modulation in the rodent brain (Allen and Allen, 1974; Diorio et al., 1993; Sapolsky et al., 1984), other structures such as septum and paraventricular thalamic nucleus are also implicated (e.g., Anthony et al., 2014; Bhatnagar and Dallman, 1998).

Few cell groups in the limbic forebrain provide substantial direct innervation of the HPA effector neurons in the PVH. However, anatomical tract-tracing studies have identified a number of candidate regions within the basal forebrain and hypothalamus that might serve as nodal points of relay between these higher-order regions and PVH (Cullinan et al., 1993; Herman et al., 2003; Roland and Sawchenko, 1993; Van de Kar and Blair, 1999). Moreover, several stress-inhibitory regions in the limbic forebrain, such as mPFC and hippocampus, give rise to predominantly excitatory glutamatergic projections (Cullinan et al., 2008; Walaas and Fonnum, 1980), suggesting that at least some of the proximate relays to PVH are inhibitory (GABAergic) in nature. Thus one organizing principle of HPA control during emotional stress is that one or multiple intermediaries provide the interface for communication between higher-order modulatory centers and pools of effector neurons. However, a complicating factor concerns the extent to which these intermediaries may serve as simple relays, as opposed to playing a more dynamic role in integrating convergent information from multiple sources before reaching the PVH. Additionally, whether the circuits charged with modulating the HPA stress axis are overlapping or distinct from those involved in behavioral adaptations, and the extent to which these pathways are differentially engaged during disparate environmental demands, have not been directly examined. Below we highlight recent studies that may illuminate these questions.

To address these issues, we first examined the nature of mPFC involvement in acute emotional stress-induced HPA activation. The rodent mPFC is implicated in a wide array of higher cognitive functions that are analogous to the primate prefrontal cortex (Wise, 2008), including decision-making, working memory, and perceptual set-shifting (Arnsten et al., 2010; Brown and Bowman, 2002; Divac, 1971; Otto and Eichenbaum, 1992). mPFC is anatomically positioned to modulate both amygdaloid and hippocampal activity, providing a means for top-down regulation of limbic information processing. Nevertheless, mPFC is also poised to modulate adaptive responses to stress via relays in the basal forebrain, hypothalamus, and midbrain (Crane et al., 2003; Myers et al., 2016; Neafsey, 1990; Radley et al., 2006a; Radley et al., 2009; Radley and Sawchenko, 2011; Sullivan and Gratton, 1999; van Eden and Buijs, 2000). In keeping with the theme of indirect limbic modulation of HPA activity, none of the mPFC subfields contain any appreciable projections to HPA effectors in PVH. Although mPFC effects on stress-induced HPA activation are generally inhibitory (Diorio et al., 1993; Figueiredo et al., 2003; Radley et al., 2009; Weinberg et al., 2010), other evidence suggests at least some degree of functional differentiation by cortical subfield (McKlveen et al., 2015; Radley et al., 2006a; Sullivan and Gratton, 1999).

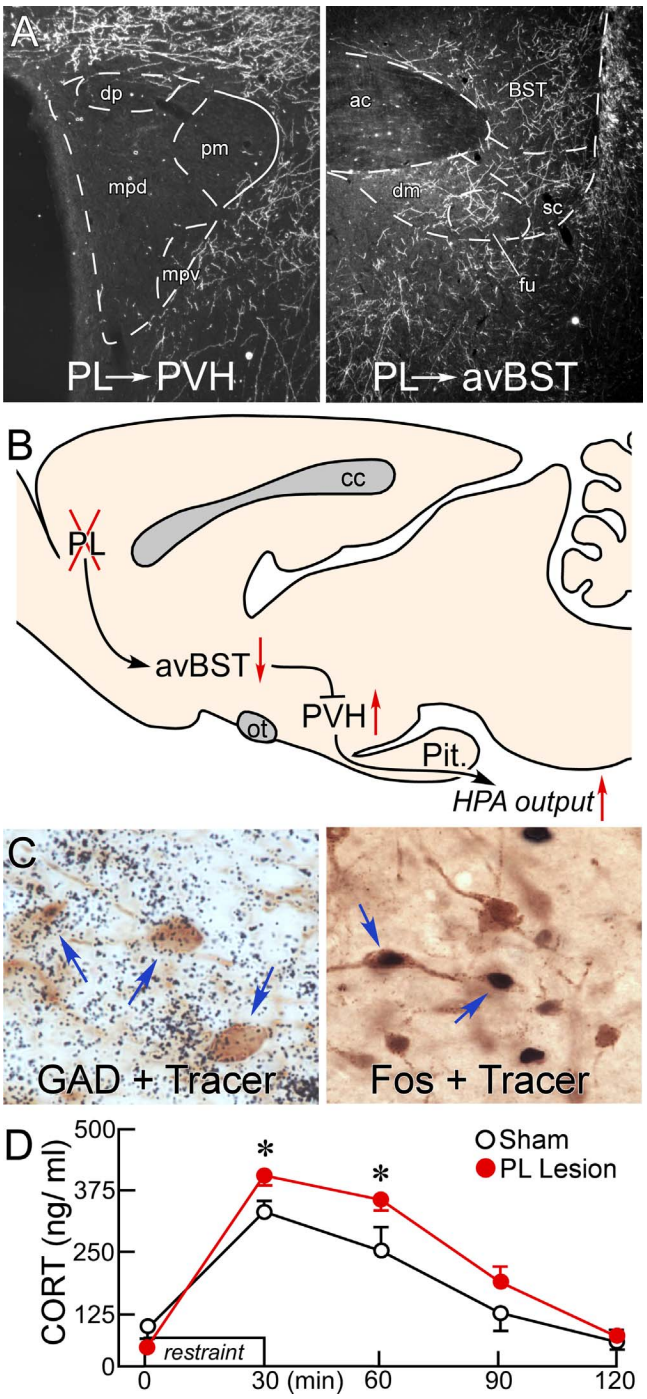

Fig. 1. Prelimbic (PL) cortical involvement in HPA axis modulation.
A. Anterograde tracer injections in PL highlight weak projections to neurosecretory neurons in medial parvicellular dorsal (mpd) division of the paraventricular hypothalamus (PVH), and more robust inputs to multiple avBST subdivisions. B. Schematic of observed connectivity between PL and avBST, and the consequences of PL lesions on functional activation of PVH/HPA output. Arrows and horizontal line indicate excitation and inhibition, respectively. C. Retrograde tracer injections in PVH labeled neurons in anteroventral bed nuclei of the stria terminalis (avBST) that are both GABAergic (express glutamate decarboxylase, GAD, mRNA) and stress-sensitive (display Fos induction). PL lesions diminished activity in GABAergic, PVH-projecting neurons in avBST, and increased HPA output (D) following 30 min of restraint stress. ac, anterior commissure; dm, dorsomedial nucleus, avBST; fu, fusiform nucleus, avBST; sc, subcommissural nucleus, avBST; dp, dorsal parvicellular division of PVH; pm, posterior magnocellular division, PVH; mpv, medial parvicellular ventral division, PVH. *, $p < 0.05$. Data are based upon Radley et al. (2009).

Multiple lines of evidence from our laboratory have identified a cluster of GABAergic (i.e., expressing mRNA for glutamic acid decarboxylase [GAD] 65 and/or 67 kDa isoforms) neurons distributed within avBST i.e., encompassing subcommissural, dorsomedial, and fusiform subdivisions as based upon Dong and colleagues (2001) that form a disynaptic relay between PL and PVH (Johnson et al., 2016; Radley, 2012; Radley et al., 2009). First, anatomical tract-tracing experiments indicated that extrinsic projections from PL converge onto stress-sensitive, PVH-projecting neurons in the avBST (Fig. 1). In rats bearing excitotoxin lesions in PL, PVH-projecting GABAergic neurons in avBST showed diminished functional (i.e., Fos) activation following acute restraint stress that corresponding with enhanced HPA activation. Follow-up experiments involving discrete immunotoxin (Radley et al., 2009) or excitotoxin injections (Johnson and Radley, unpublished observations) centered within avBST produced augmented HPA activation in response to acute stressors (restraint and tail suspension). Finally, optogenetic silencing and activation of avBST cell bodies during 10 min of tail suspension augmented and attenuated HPA activation, respectively (Fig. 2) (Johnson et al., 2016).

It is important to note that, although the vast majority (> 90%) of avBST neurons are GABAergic (Cullinan et al., 1993; Poulin et al., 2009; Kudo et al., 2012), there is also evidence for a small subpopulation of glutamatergic neurons (Hur and Zaborsky, 2005; Poulin et al., 2009; Kudo et al., 2012), some of which are PVH-projecting (Csáki et al., 2000). In spite of this small proportional representation, avBST glutamatergic neurons have been implicated in several different physiological and behavioral contexts (Georges and Aston-Jones, 2001, 2002; Jalabert et al., 2009; Choi et al., 2007; Jennings et al., 2013). Nevertheless, the anatomical and functional evidence that we have gathered endorses a predominantly GABAergic inhibitory phenotype with regard to stress-modulatory circuitry that we have described. First, our quantification of PVH-projecting neurons in avBST identified via retrograde labeling showed that 86% expressed GAD mRNA (Radley and Sawchenko, 2011). Confocal laser-scanning microscopic analysis of anterogradely-labeled axons and terminals in PVH revealed extensive (87%) immunolocalization with the GABA synthetic enzyme GAD-65, and notably in close apposition to CRF-immunoreactive secretory neurons (Fig. 2)(Johnson et al., 2016). By contrast, immunohistochemical staining for vGLUT2 revealed no colocalization with YFP-positive terminals originating in avBST (Johnson et al., 2016).

Subsequent evidence suggests that avBST figures more prominently in integrating, rather than merely relaying, information from multiple limbic forebrain cell groups in modulating stress-induced HPA activity. Past work of ours employing tract-tracing and functional neuroanatomical approaches endorses two important themes regarding avBST modulation of the HPA stress axis: (1) that it receives convergent inputs from multiple limbic forebrain cell groups implicated in HPA inhibition; (2) it is capable of integrating these influences (Radley and Sawchenko, 2011) (Fig. 3). For example, rats bearing excitotoxin lesions in the ventral subiculum (vSUB; i.e., the portion of the hippocampal formation that provides the bulk of subcortical outputs from hippocampus proper) showed similar diminished functional activation (i.e., as following PL lesions) in GABAergic PVH-afferent cell groups in avBST following acute restraint stress as well as increased CRF mRNA in PVH proper. In the same series of experiments, vSUB lesions were also noted to increase restraint-induced HPA activation, as previously reported (Herman et al., 1995b; Herman et al., 1992). Animals given dual anterograde tracer injections in PL and vSUB, and a retrograde tracer injection into PVH, revealed extensive convergence between PL and vSUB terminal fields and stress-sensitive PVH-projecting cell groups throughout avBST. Next, rats bearing dual excitotoxin lesions of both PL and vSUB were found to exhibit more exaggerated central indices of stress-induced HPA responses (i.e., CRF mRNA and AVP hnRNA expression in PVH) as compared to lesions of only PL. Finally, ablation of GABAergic cell groups in avBST produced a greater enhancement of HPA activation in response to acute restraint, as compared to animals with vSUB

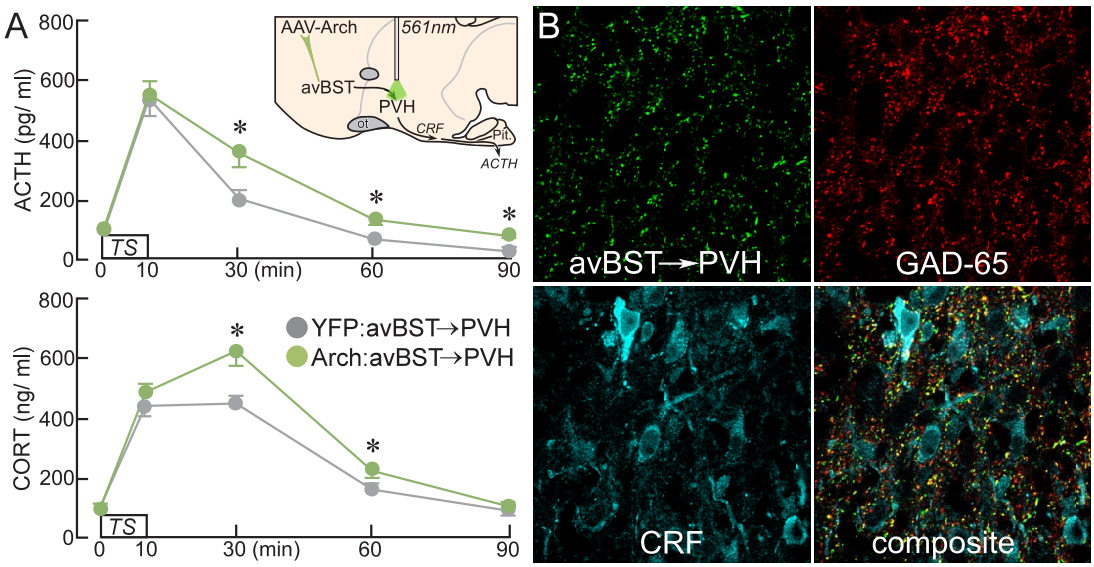

Fig. 2. Functional and phenotypic characterization of avBST inputs to PVH.
A. Photoinhibition of Archaerhodopsin-expressing (Arch) avBST-projecting terminal fields in PVH during 10 min tail suspension (TS) stress disinhibited the HPA axis as measured by adrenocorticotropin releasing hormone (ACTH, top left) and corticosterone (CORT, lower left) levels. *, $p < 0.05$. B. Top left panel depicts high magnification photomicrograph of YFP-fluorescent terminals originating from AAV-transfected avBST neuronal somata. Immunohistochemical staining for glutamate decarboxylase 65 kDa isoform (GAD-65, top right), a marker of GABAergic axons and terminals, and corticotropin releasing factor (CRF, lower left) revealed that avBST → PVH terminals are GABAergic and reside in close apposition to CRF-positive neurosecretory neurons (composite, lower right). These data highlight an inhibitory pathway from avBST to HPA effector neurons. Data are based upon Johnson et al. (2016).

lesions alone. Collectively, these studies support the idea that avBST is positioned, not merely as a relay for, but as a key integrator of HPA-inhibitory influences emanating from the limbic cortex.

While additional basal forebrain and/or hypothalamic regions are likely to act as relays of limbic cortical information in parallel with avBST for conveyance to PVH/HPA modulation (e.g., see Cullinan et al., 1993; Dayas et al., 1999; Myers et al., 2016; Nyhuis et al., 2016a), the current studies highlight several important ideas. First, our studies have localized an important source of HPA-inhibitory influences of BST to within the anteroventral subdivision, and thus provide a functional distinction between ventral and dorsal (autonomic/behavioral) subregions of BST. Second, it was not appreciated from past studies that information from the limbic forebrain converges onto a circumscribed cell group within the basal forebrain. This “convergence” model contrasts with other possible di-/multi-synaptic arrangements that have been proposed to account for how limbic forebrain regions may interface with and modulate PVH (Cullinan et al., 1993; Roland and Sawchenko, 1993; Ulrich-Lai and Herman, 2009; Van de Kar and Blair, 1999). Third, is the prospect that intermediaries between the limbic forebrain and PVH are not simply relays or signal converters (e.g., from excitation to inhibition), but play an important role in integrating stress-related information.

Another consideration is the fact that, in addition to the highlighted circuitry, much of the limbic forebrain network is inhibitory in nature, yet its modulatory influences appear to be manifest only during stressor exposure. On the one hand it is clear that PVH receives excitatory glutamatergic input (Boudaba et al., 1997; Cole and Sawchenko, 2002; Flak et al., 2009), yet the identity of the neural pathways accounting for HPA activation during emotional stressors has not been forthcoming (although for insight into this issue, see Hewitt et al., 2009; Nyhuis et al., 2016b). Finally, as will be discussed below, the existence of a neural hub for the integration of descending influences on neuroendocrine output may have important implications for understanding how such responses are coordinated with behavioral adaptations during acute stress, and how synaptic and functional alterations in this circuit may account for differential adaptations following chronic or protracted challenges.

3. Expansion of HPA-modulatory circuit concept to stress coping behavior

When animals and humans are exposed to threatening or stressful situations, they demonstrate a set of highly conserved defensive behavioral responses designed to promote adaptation. In rodents, each of these response strategies involves the engagement of neural systems that mediate active (defensive, escape) or passive (immobility, freezing) behaviors (Keay and Bandler, 2001). Links between behavioral response strategies and HPA activity are based upon numerous observations that active and passive behaviors relate with low and high HPA activity, respectively (Koolhaas, 2008; Veenema et al., 2004; Veenema et al., 2003; Walker et al., 2009a). Moreover, individual variability in these response “types” (especially passive coping and elevated HPA activity) are widely regarded to increase susceptibility for stress-related diseases (de Kloet et al., 2005; Koolhaas et al., 2007; Koolhaas et al., 1999; Olff, 1999). The existence of coping styles that may combine HPA reactivity with specific types of behavioral responses raises the possibility that a common neural circuit in the brain may subserve or bias responses toward a specific direction. Relative to our discussion in the foregoing section, cell groups that also relay information between the limbic forebrain and PVH would serve as candidates for modulating behavioral response strategies in tandem with HPA activity. In this regard, we will summarize recent work providing an early indication that avBST may be an important component for a system coordinating these responses. Our discussion will focus on neural circuitry modulating responses during inescapable challenges; excellent surveys are available that highlight neural mechanisms in response to escapable/controllable stressors (Amat et al., 2005; Maier and Watkins, 2005, 2010).

There is an extensive literature implicating the dorsal BST in the regulation of behavioral and autonomic responses to sustained threats and/or contextual fear conditioning collectively likened to “anxiety” (Davis et al., 2010; Kim et al., 2013; Sullivan et al., 2004; Walker and Davis, 1997; Walker et al., 2003a). Given the reciprocal interactions between dorsal BST and the amygdaloid complex on the one hand, and interconnections with midbrain and medullary structures important for

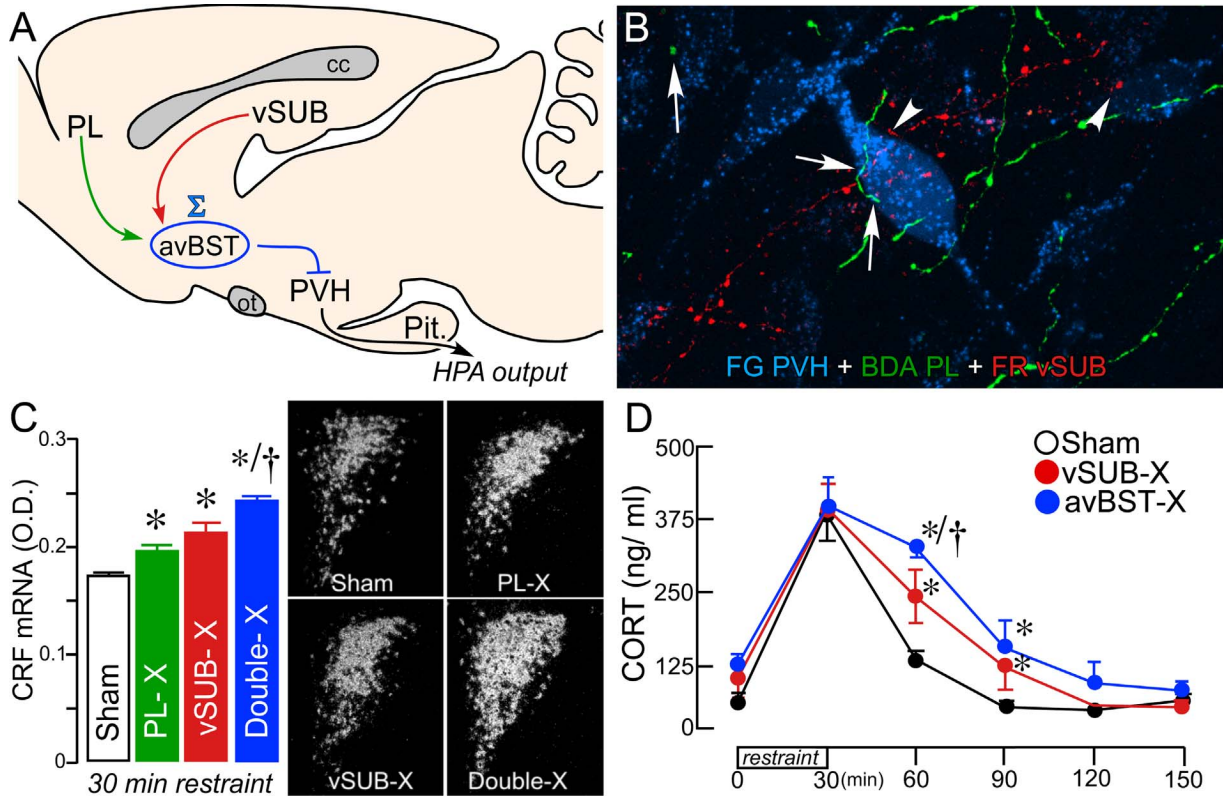

Fig. 3. Integration and additivity of convergent HPA-inhibitory limbic influences via avBST.
A. Schematic circuit model wherein the prelimbic cortex (PL, green) and ventral subiculum (vSUB, red) inputs are integrated within avBST for the inhibition of HPA output. B. Convergence of FluoroRuby-filled vSUB terminals (FR, red) and biotinylated dextran amine-positive (BDA, green) originating from PL onto PVH-projecting avBST neurons retrogradely labeled with Fluoro-Gold (FG, blue). C. CRF mRNA levels in PVH in animals bearing PL or vSUB lesions are greater than in sham controls, whereas lesions of both PL and vSUB (Double-X) show a further enhancement. D. Rats with GABAergic elements of avBST disrupted (i.e., avBST-X) exhibited elevated peripheral HPA output relative to both vSUB and sham-lesioned animals after 30 min restraint stress. (*, $p < 0.05$ lesion vs sham group; †, $p < 0.05$ Double or avBST lesion versus single PL or vSUB lesion groups). Data are based upon Radley and Sawchenko (2011).

autonomic and defensive behavioral responses on the other, this structure is well-positioned to modulate adaptive responses to immediate challenges and in contexts that demand temporally precise and rapid reactions. Less well appreciated is that, although ventral aspects of BST issue projections to autonomic and behavioral output centers, they also provide extensive innervation of the neuroendocrine effector cell groups within the PVH that may be more important for adaptations to more protracted challenges. Relative to dorsal BST (i.e., the nuclei dorsal to the anterior commissure), the ventral counterpart receives a much wider array of inputs from cell groups important for emotional regulation (e.g., mPFC, ventral subiculum, paraventricular thalamus) (Dong et al., 2001; Dong and Swanson, 2006; Radley and Sawchenko, 2011). Thus, the ventral BST would seem well-positioned for coordinating behavioral and endocrine responses to sustained challenges (Cecchi et al., 2002), and its receiving of extensive limbic forebrain inputs could support ongoing reappraisals and iteratively optimize adaptation.

A variety of neural circuits have been implicated in modulating coping responses, although the midbrain periaqueductal gray area is prominent in this regard with its dorsal and ventral longitudinal cell columns supporting active and passive behaviors respectively (Keay and Bandler, 2001). Recent work has confirmed and expanded on long-held notions of PAG function in behavioral response strategies (Bandler and Shipley, 1994; Ledoux et al., 1988). These results highlight involvement of the ventrolateral subdivision in freezing (Assareh et al., 2016) via efferents from the central nucleus of the amygdala and vlPAG afferents to the medulla (Tovote et al., 2016). Additionally, previous studies have shown that lesions encompassing avBST are capable of impairing active coping responses to acute stressors (Henke, 1984; Schulz and Canbeyli, 2000), whereas tract-tracing evidence supports an avBST → vlPAG pathway (Dong et al., 2001; Dong and Swanson, 2006) that could modulate these behavioral responses.

Recent work of ours has shown that avBST GABAergic inputs into vlPAG are activated during inescapable challenges to inhibit immobility in tail suspension and forced swim tests, and thus implicate this pathway in the gating of passive behavioral strategies. Whereas these tests have been classically employed to study “depression-like” behaviors, evidence increasingly suggests that these challenges are more appropriate for understanding stress adaptation and coping (de Boer et al., 2016; de Kloet and Molendijk, 2016; Molendijk and de Kloet, 2015). For example, optogenetic silencing of avBST neurons increased immobility and augmented HPA output during a 10-min tail suspension challenge (Fig. 4) (Johnson et al., 2016). Follow-up experiments demonstrated that avBST inputs into vlPAG are predominantly GABAergic, and inactivation of this axonal pathway increased immobility and passive floating in tail suspension and forced swim tests, respectively (Johnson et al., 2016). Inactivation of either avBST axonal inputs into PVH or vlPAG, were found to impact only HPA or behavioral output, respectively, and further support for the dissociabilty of these pathways was gleaned from dual retrograde tract-tracing experiments showing that each arises from comingled yet largely distinct cell populations in avBST (Fig. 5). Because most of the GABAergic efferents from avBST to PAG terminate preferentially within the ventrolateral subdivision and only sparsely to dorsolateral and dorsal subdivisions (Dong et al., 2001; Dong and Swanson, 2006; Johnson et al., 2016), this suggests that inactivating this pathway disengages the inhibitory influence on passive coping that is normally provided during acute challenges. An important next step will be to understand how the limbic

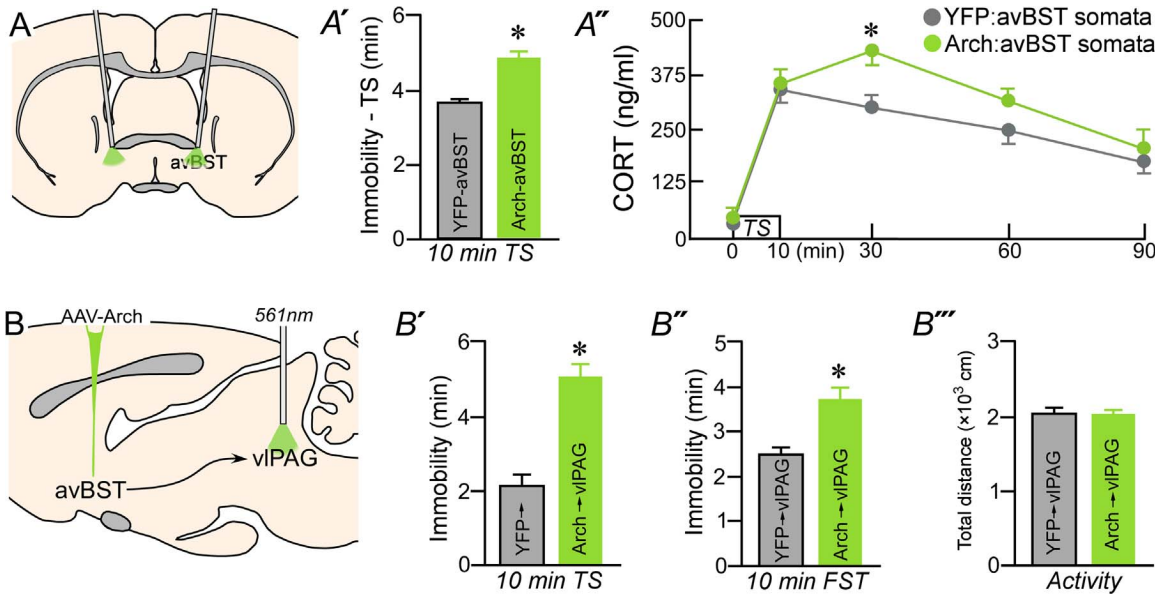

Fig. 4. Acute manipulations of avBST neuronal activity during emotional stress reveal its involvement in both behavioral and endocrine stress responses.
A. Diagram depicting 561 nm laser illumination of AAV-Arch expressing neurons in avBST. *A′*. Photoinhibition of avBST neurons increased both behavioral immobility and augmented HPA output (*A″*) during tail suspension (TS). B. Schematic depicting AAV-Arch microinjection into avBST and subsequent photoinhibition of the axonal pathway from avBST to the ventrolateral periaqueductal gray (vlPAG). Photoinhibition of avBST terminals in vlPAG was associated with increased immobility during tail suspension (*B′*) as well as during the forced swim test (FST, *B″*), while general locomotor activity was unchanged (*B‴*). *, $p < 0.05$. Data are based upon Johnson et al. (2016).

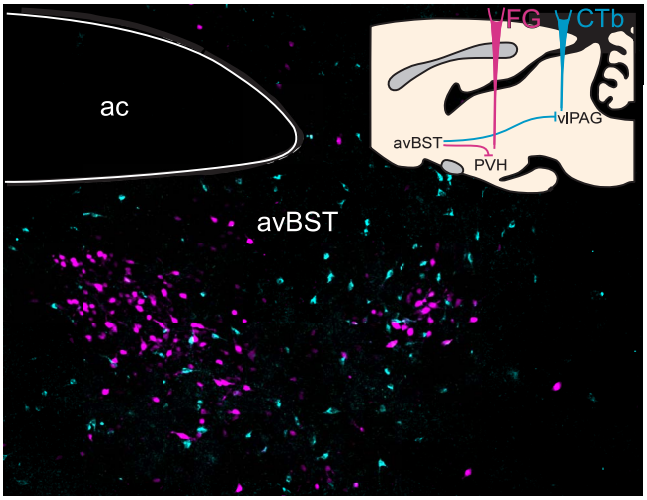

Fig. 5. Anatomical evidence that distinct subpopulations of avBST neurons give rise to HPA and behavioral modulation.
Dual microinjection of Fluoro-Gold (FG, magenta) in PVH and cholera toxin B subunit (CTb, cyan) in vlPAG (inset diagram) followed by retrograde transport of each tracer revealed intermingled, but non-overlapping populations of PVH- and vlPAG-projecting neurons in avBST.

forebrain modulates avBST circuitry charged with coordinating behavioral and endocrine adjustments in response to stressors. Past studies have implicated mPFC and vSUB in differentially modulating behavioral coping strategies (Jett et al., 2015; Shah et al., 2004), although the circuit basis of this modulation in the context of HPA activity, and avBST involvement, each deserve further scrutiny.

4. Mechanisms of modulation following repeated stress exposure

Chronic stress produces a constellation of behavioral, endocrine and physiological changes in laboratory animals that have been shown to increase vulnerability to future insults, and as such are likened to increased diseased susceptibility in humans following stress exposure (Chrousos, 2000; Essex et al., 2002; Heim et al., 2008; McEwen, 2000; Pasternac and Talajic, 1991; Shively et al., 2009). Although there exists a wide range of variability in human cortisol response patterns (Kirschbaum et al., 1995; Kudielka and Wust, 2010), these data are generally consistent with animal studies suggesting that HPA axis responses tend to decline upon repeated exposure to the same (homotypic) stressor, but may be maintained during certain challenges, or may increase in responses to a novel (heterotypic) challenge (Bhatnagar and Dallman, 1998; Dallman, 1993; Dallman et al., 1992; Herman et al., 1995a; Ottenweller et al., 1989). These phenomena of HPA axis habituation and sensitization, represent adaptations to chronic stress that are highly relevant to understanding and managing the negative health consequences of chronic stress exposure. In the behavioral dimension, alterations in response to chronic stress are generally understood along the lines of shifting from active to more passive coping strategies (de Kloet and Molendijk, 2016; Jett et al., 2015; Roth et al., 2012; Tye et al., 2013), as such changes are evoked from protracted challenges or stimuli whereby active strategies fail to effectively deal with the threat at hand (Overmier and Seligman, 1967; Pavlov, 1927; Seligman, 1968; Seligman and Maier, 1967; Seligman et al., 1968; Steimer, 2011). Along these lines, HPA axis and passive coping alterations may be integral aspects of a response set following chronic stress exposure that promotes near-term adaptation at the long-term cost of increased susceptibility to subsequent stress exposure and stress-related diseases (McEwen and Gianaros, 2011).

Multiple limbic forebrain regions undergo dendritic and synaptic remodeling that are believed to play an important role in the behavioral and endocrine modifications in response to repeated stressors (Radley et al., 2006b). This synaptic reorganization is commonly regarded as integral to the concepts of allostasis and allostatic load (and similar to Selye's heterostasis; Selye, 1973) following chronic stress (McEwen and Wingfield, 2003), whereby such modifications promote adaptation for survival but at the cost of increased disease susceptibility (McEwen and Gianaros, 2011). From the perspective of avBST stress-modulatory functions, regressive plasticity in elements of upstream limbic forebrain regions may be critically important for biasing these circuits toward permitting enhanced HPA activity and increased passive coping behaviors. For example, we observed that avBST-projecting neurons in mPFC showed a greater degree of dendritic spine synaptic attrition than

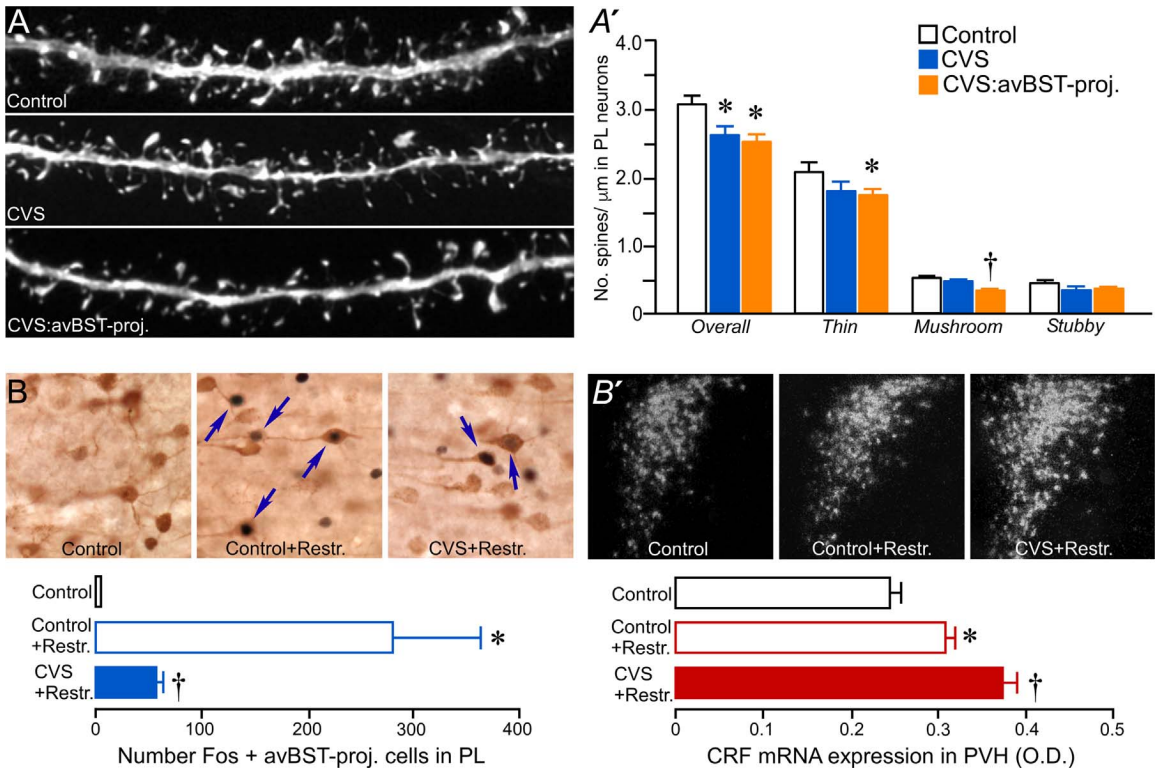

Fig. 6. Regressive changes in mPFC → avBST pathway following 14 days of chronic variable stress (CVS).
A. Representative photomicrographs of pyramidal neuron dendritic segments in PL filled with the fluorescent dye, Lucifer yellow. *A′*. Quantification of dendritic spine densities indicated that CVS exposure led to synaptic attrition in PL, manifested in decreased overall spine density, and particularly within thin subtypes (*, $p < 0.05$). By contrast, CVS-induced decrements in large mushroom spines were observed only in avBST-projecting PL neurons (†, $p < 0.05$ vs non avBST-projecting neurons). B. avBST-projecting PL neurons experienced marked Fos induction in stress-naïve, acutely restrained rats (*, $p < 0.05$ vs unstressed control group), however this index was significantly reduced in animals with a history of CVS (†, $p < 0.05$ vs acute stress control). *B′*. 30 min restraint stress exposure also led to increased CRF mRNA expression in PVH (*, $p < 0.05$ vs unstressed control), while this measure was further enhanced in rats with a history of CVS (†, $p < 0.05$ vs stressed control group). These data are consistent with the premise that CVS-induced decrements in this circuit may account for augmented HPA activity. Data adapted from Radley et al. (2013).

non-BST projecting neurons in the mPFC following two weeks of chronic variable stress exposure (Radley et al., 2013). Follow-up functional anatomical experiments linked decreased immediate-early gene induction in avBST-projecting PL neurons to HPA sensitization after a novel restraint-stress challenge in animals previously subjected to chronic stress (Fig. 6). Although vSUB neurons (i.e., avBST-projecting and other) did not undergo any dendritic spine reorganization following chronic stress exposure (Radley et al., 2013), the subpopulation of neurons projecting to avBST showed diminished functional activation in response to a subsequent novel stressor (Radley and Sawchenko, 2015).

These findings illustrate the idea that limbic-avBST inputs are differentially vulnerable to chronic stress exposure, and thus may define a mechanism for selective structural and activational network changes that could promote shifts in coping styles that are commensurate with adaptation under protracted inescapable challenges (Fig. 7). More work is needed to directly test the roles for these pathways following chronic stress, and importantly, the extent to which circuit perturbations involving avBST contrast with other components of the limbic forebrain network for differentially impacting behavioral and endocrine responses.

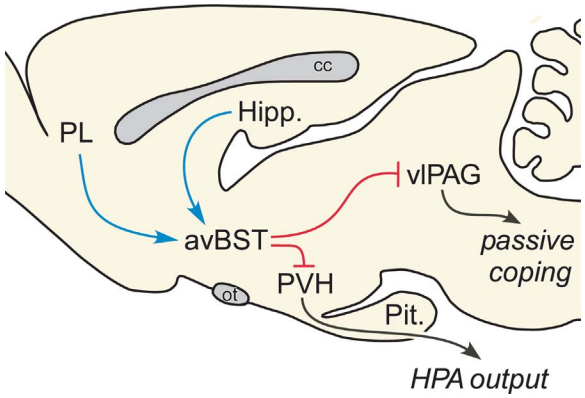

Fig. 7. Proposed circuit accounting for top-down limbic cortical coordination of HPA output with passive behavioral strategies.
Red lines terminating in "T" (inhibitory) and blue lines terminating in arrows (excitatory) summarize the circuitry highlighted in this review. We propose that avBST may integrate activity from upstream limbic cortical regions, such as PL and vSUB, to modulate HPA outputand behavioral response strategies during acute challenges. This circuit may also contribute to our understanding of how limbic cortical perturbations may promote shifts in response strategies leading to resilience (high activity) or vulnerability (low activity). cc, corpus callosum; Hipp., hippocampus; ot, optic tract; Pit., pituitary gland.

5. Discussion and future directions

Circuit organizational aspects

Aside from several previous reports that have suggested a common neural substrate for modulation of HPA and behavioral responses to stress (Cecchi et al., 2002; de Boer et al., 2016), much of the work in the stress field has been focused on elucidating the mechanisms of neuroendocrine or behavior responses in isolation from one another. Our work implicates avBST as a neural hub for coordinating restraining influences on both the HPA axis and passive behavioral responses to inescapable challenges via divergent GABAergic pathways to PVH and vlPAG. A critical element of avBST function also involves its capacity to

integrate upstream limbic forebrain information to coordinate the modulation of downstream neuroendocrine and behavioral responses during stress, and suggests several important organizational principles and perspectives for future studies.

As noted previously, mPFC influences over the HPA axis require one or multiple intermediaries (i.e., avBST) for the modulation of HPA axis activity. By contrast, prefrontal modulation of defensive behavior can bypass the basal forebrain to more directly modulate behavioral responses (Challis et al., 2014; Franklin et al., 2017; Warden et al., 2012), as mPFC issues axonal inputs into multiple subdivisions of PAG (Floyd et al., 2000; Franklin et al., 2017). Pathways involving VTA dopaminergic neurons, that may or may not be distinct from prefrontal circuitry, are capable of driving shifts in active-to-passive behaviors during inescapable stress exposure (Chaudhury et al., 2013; Tye et al., 2013). Nevertheless, the prefrontal-avBST pathway would afford a coordinating capability of responses across endocrine and behavioral domains, which may be separable from, but carried out in parallel to the direct mPFC-midbrain and VTA pathways that control behavior in a more temporally specific manner (Tye et al., 2013; Warden et al., 2012). From this standpoint, differences in the activity of the prefrontal-avBST pathway could bias the organism toward different response strategies or coping styles, whereas altered activity may underlie shifts that bias response strategies for adaptation to changing environmental conditions, such following chronic stress exposure.

The modulatory nature of avBST circuitry is further conferred by the fact that manipulations on the order of minutes, not seconds, are required to observe overt changes in endocrine and behavioral responses (Johnson et al., 2016). This is particularly true with regard to modulation of the HPA axis, whereby short-term manipulations of the avBST-PVH pathway, such as over the course of a 10-min period of stress exposure, are not manifest immediately but ensue over the next 15–30 min. One possible explanation is that the time course involving the accumulation and reduction of levels of blood hormones is slower such that effects of rapidly altering neural activity in HPA-modulatory pathways are not immediately observable. Another possibility involves some relationship with rapid glucocorticoid (i.e., nongenomic) receptor-mediated feedback within avBST and/or PVH (Dallman, 2005; Ginsberg et al., 2003; Keller-Wood, 2015; Tasker and Herman, 2011), such that differential activity in this pathway may enhance or shunt steroidal negative-feedback influences on HPA activity.

The role of avBST inputs, within the broader array of circuitry impinging on PVH neurosecretory neurons and other behavioral/autonomic effector systems, remains to be fully explored. Establishing stressor specificity, or lack thereof, as well as boundary conditions for involvement within a given stressor may provide insights into whether avBST or similar circuits function within defined roles or act more generically, even redundantly, for control of stress responses. Investigating the functional role of such pathways within specific stress paradigms (e.g., repeated homotypic or chronic variable stress) has already begun to inform our understanding these systems. Our circuit manipulations under acute inescapable stressors, and the broader literature, indicate that maladaptive changes following chronic stress are due at least in part to withdrawal of top-down inhibitory control. Further investigation is also needed to establish a circuit-level understanding of whether increased drive within parallel pathways, to either the HPA axis or behavioral effector systems, occurs alongside the withdrawal of limbic cortical inhibitory influences following chronic stress.

Relevance to coping styles

Another future direction of interest involves understanding the contribution of differential activity in avBST circuitry in relation to coping styles proposed to exist in animals and humans (de Boer et al., 2016; Korte et al., 2005). Studies have observed correlations wherein rodents that tend toward aggression and/or *proactive* coping also mount the lowest HPA responses to stressors, whereas rodents with low aggression and/or *reactive* coping show higher HPA output (Bohus et al., 1987; Henry, 1992; Henry and Stephens, 1977; Koolhaas et al., 1999; Sluyter et al., 1996; Veenema et al., 2004; Veenema et al., 2003; Walker et al., 2009b). Along similar lines, female rodents display larger increases in corticosterone secretion (Goel et al., 2014; Viau et al., 2005), and use different behavioral strategies than males in response to a variety of challenges (Goel et al., 2014; Mueller and Bale, 2008; Shansky and Woolley, 2016; Viau et al., 2005). Experimental manipulations that force passive coping strategies have also been shown to enhance HPA output (De Boer et al., 1990; Korte et al., 1992). Together, these findings support a potential mechanism wherein HPA output and passive behavioral coping may be modulated in a coordinated manner as a function of trait variability, sex-specificity, and environmental conditions.

Whether the avBST and related circuitry described herein provide a neural substrate for understanding coping styles remains to be carefully examined. One possibility is that activation of this circuit does not promote proactive coping styles *per se*, but instead restrains HPA and passive behaviors to counteract an otherwise more reactive response pattern. Another scenario is that inhibition of this circuit could be constitutively active or more readily or enabled in rodents that naturally display a more reactive coping style. Finally, the existence of a neural hub that coordinates the inhibition of passive coping behavior while concurrently restraining HPA output has teleological significance. This idea is derived from evidence that different behavioral strategies require distinct physiological and endocrine adjustments (Henry, 1992; Henry and Stephens, 1977; Korte et al., 2005; Mason, 1972; Mason et al., 1976; Ursin et al., 1977). That avBST exhibits the property of inhibiting HPA activity in conjunction with passive behaviors, suggests that the coordination of these functions likely confers an adaptive advantage in certain environmental contexts. In that vein, reactive coping is generally thought to be an advantageous response to inescapable challenges in that it conserves energy that could be better deployed at later time if the situation changes (Mason et al., 1976; Korte et al., 2005). Should the proactive coping style fail (i.e. in inescapable situations), it may be more beneficial to redirect these resources toward survival systems via increased activation of the HPA axis. Conversely, avBST may play a role in promoting the opposite set of responses at the outset, or during later reappraisals of the stressful event, wherein active coping and diminished HPA output might have benefits of their own. The continuum of coping styles, perhaps reflected in avBST response capacity, might then represent biases toward strategies that have value in environments with varying exposures to prolonged or inescapable stress. Finally, it is also notable that chronic stress paradigms generally bias animals toward reactive coping strategies, which suggests that, rather than strictly adhering to one “style,” the underlying systems are capable of adapting to the shifting environmental demands.

Parcellation of BST in stress-related psychiatric disorders

In recent years increasing scrutiny has been given to BST dysregulation in stress-related psychiatric illnesses (e.g., see Daniel and Rainnie, 2016; Fox et al., 2015; Hammack and May, 2015; Lebow and Chen, 2016; Shackman and Fox, 2016), although much of this focus has been in the context of anxiety-related and post-traumatic stress disorders. Another recent trend also reflects the increasing awareness that the BST is highly complex and heterogeneous, containing multiple distinct structural and functional domains important for different aspects of stress regulation (Crestani et al., 2013; Daniel and Rainnie, 2016; Gungor and Pare, 2016; Lebow and Chen, 2016; Sparta et al., 2013; Vranjkovic et al., 2017). While not discussed here, converging evidence suggests that the dorsal BST, along with the central nucleus of the amygdala, forms a network prominently implicated in the regulation of anxiety-like, behavioral, and autonomic responses under a range of environmental challenges and stressors (Johnson et al., 2008; Kim

et al., 2013; Walker and Davis, 1997; Walker et al., 2003a). Although avBST is an important component in the "central extended amygdala" network (Alheid and Heimer, 1988; Fox et al., 2015; Swanson and Petrovich, 1998; Ursin et al., 1977; Walker et al., 2003b), it is distinguished from other elements by its capacity to directly modulate neuroendocrine functions. Moreover, the capacity avBST to coordinate HPA and behavioral coping responses suggests an involvement in different aspects of adaptive responses that have not been previously contrasted from its dorsal counterpart. avBST involvement in anxiety-like behaviors has been demonstrated (Glangetas et al., 2017; Jennings et al., 2013; Marcinkiewcz et al., 2016), but both the intrinsic connectivity between dorsal and ventral BST, and comorbidity of anxiety and depression disorders may implicate avBST as a locus in such instances. Regardless, given the robust autonomic correlates with post-traumatic stress and anxiety disorders, and neuroendocrine disturbances in depressive disorders (recently summarized in Fink, 2017), we speculate that the outcomes of BST dysfunction differ regionally, with dorsal and ventral dysfunctional accounting for anxiety- and depression-like responses, respectively. Such an oversimplification of BST necessarily fails to capture its structural and functional complexity, however, it should serve as a useful perspective for considering BST sub-circuitry in more specific psychiatric contexts in future animal and human studies.

Conflicts of interest

The authors, Jason Radley and Shane Johnson, have no conflicts of interest to report.

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