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Invited review

The bed nucleus of the stria terminalis in drug-associated behavior and affect: A circuit-based perspective

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ABSTRACT

The bed nucleus of the stria terminalis was first described nearly a century ago and has since emerged as a region central to motivated behavior and affective states. The last several decades have firmly established a role for the BNST in drug-associated behavior and implicated this region in addiction-related processes. Whereas past approaches used to characterize the BNST have focused on a more general role of this region and its subnuclei in behavior, more recent work has begun to reveal its elaborate circuitry and cellular components. Such recent developments are largely owed to methodological advances, which have made possible efforts previously deemed intractable, such as tracing of long-range cell-type specific projections and identifying functional efferent and afferent connections. In this review, we integrate earlier foundational work with more recent and advanced studies to construct a broad overview of the molecular neurocircuitry of the BNST in drug-associated behavior and affect.

This article is part of the Special Issue entitled “Alcoholism”.

Contents

1. Introduction

The bed nucleus of the stria terminalis (BNST) was first anatomically defined in 1923 by Johnston, who described the structure as a “band or ridge of gray matter lying medial to the caudate nucleus” (Johnston, 1923, see Fig. 1). Nearly a century later, this structure has been identified as a key regulator of several

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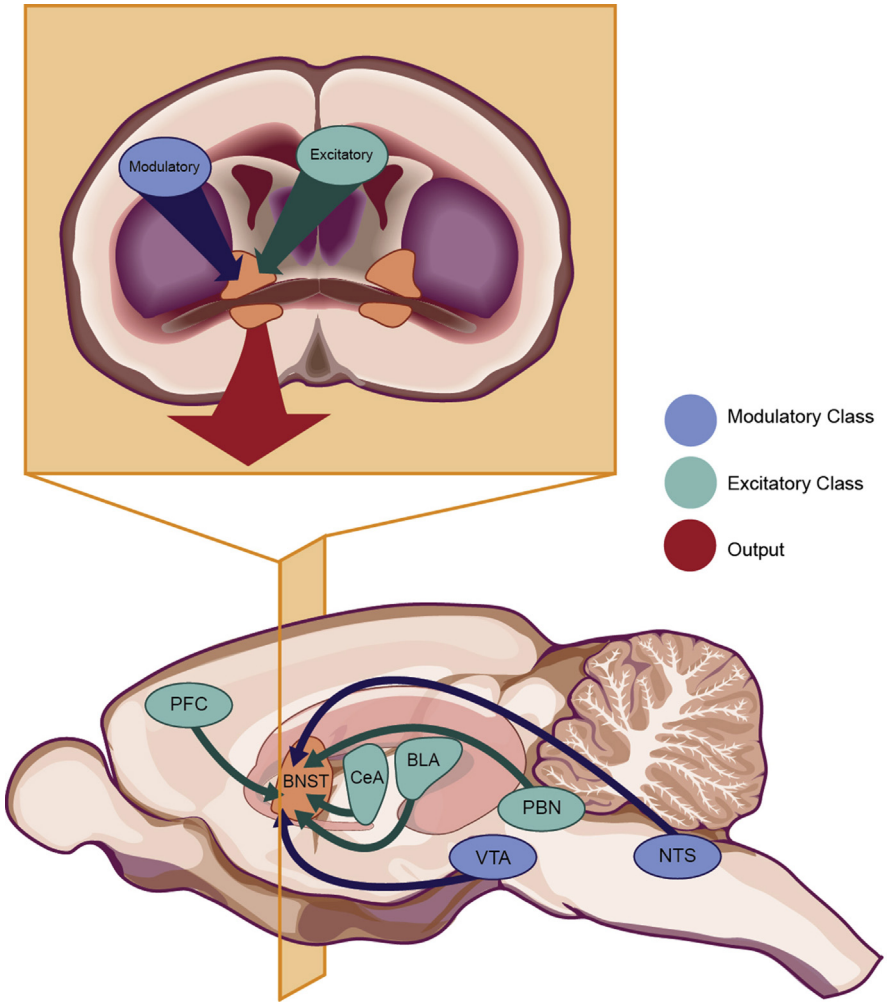

Fig. 1. Schematic of rodent bed nucleus of the stria terminalis in coronal (top) and sagittal planes (bottom).

motivational states and affective modalities, including anxiety, fear, aversion, stress, and reward (reviewed in Lebow and Chen, 2016). Although work over the last several decades has implicated the BNST in a broad range of affective states and behaviors, optogenetic and chemogenetic advances have more recently allowed researchers to elucidate the cell-type and circuit-specific mechanisms underlying its involvement. This shift in focus from a broad region-based perspective to a cell type- and circuit-specific understanding of complex behavioral states is largely owed to the advent of modern genetic and viral tools. Thus, a more complex anatomical picture of the BNST has developed and insight into its intrinsic and extrinsic pathways has been gained.

Since the early work of Johnston, the anatomical organization of the BNST has been refined and efforts have been made to characterize its cyto- and chemo-architecture. Surrounding the more caudal aspect of the anterior commissure and forming a major subdivision of the extended amygdala forebrain continuum, the BNST is a dense collection of small yet distinct nuclei (Alheid, 2003; Alheid et al., 1998; De Olmos et al., 2004). Neuroanatomical studies in the rodent have identified 12–18 distinct subdivisions of the BNST, based on patterns of molecular expression and neuronal composition (Bota et al., 2012; Ju and Swanson, 1989). There is proposed to be a considerable amount of local connectivity among the subregions of the BNST as described by Dong and Swanson (2004, 2006a,b), and studies have just recently started to examine the functional neuroconnectivity of the BNST microcircuitry. In the sections that follow, the intricate neurochemical composition of the BNST and its adjunctive intrinsic and extrinsic circuits, along with their known contributions to diverse behaviors are described, with particular focus on the dorsal lateral and ventral BNST.

2. Intrinsic composition of the BNST

The BNST is a diverse structure comprised of many distinct nuclei broadly categorized into an anterior-posterior (initially medial-lateral) division (Bota and Swanson, 2010; Ju and Swanson, 1989; Krettek and Price, 1978) and further subdivided into a dorsal-ventral division along the anterior portion (Ju and Swanson, 1989; Ju et al., 1989). Neurons within these divisions and their subnuclei co-express a variety of signaling molecules, including neuropeptides such as: corticotropin-releasing factor (CRF), dynorphin, enkephalin, neuropeptide Y, neurotensin, relaxin, and somatostatin (Ju et al., 1989; Poulin et al., 2009; Walter et al., 1991). The majority of BNST neurons are GABAergic in phenotype (Cullinan et al., 1993; Esclapez et al., 1993), with modest expression of glutamate cells in the posterior BNST and a sparse population in the dorsomedial and fusiform nuclei (Poulin et al., 2009). These BNST neurons are densely innervated by a variety of neuromodulatory centers described below.