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New Developments and Future Directions in Understanding Locus Coeruleus – Norepinephrine (LC-NE) Function

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This interesting collection of articles both reviews and brings into focus the existing literature dealing with LC-NE impacts on sensory processing and some consequent roles in shaping sensory-dependent behavior. There are also new, mostly early-stage data presented in some of the articles that raise provocative questions about LC organization and function. A major issue common to many of the articles in this collection concerns the extent to which the LC-NE system displays heterogeneity in terms of its anatomical organization, discharge properties and actions across and within terminal fields.

In this commentary, rather than review the information contained in each article, we attempt to use these articles to identify a set of major issues that will need to be addressed as the field moves forward. Each issue is presented below as a question for stimulating hypotheses that could guide future studies. Data presented in the articles in this issue and elsewhere provide clues to answers to these questions. However, at the present time the available data typically provide only partial answers that primarily serve to bring questions more sharply into focus and can serve to prioritize future research.

How modularized is the LC?

The earliest observations of LC emphasized its small number of neurons, characterized by the same putative neurotransmitter that provided massively arborized projections innervating multiple brain regions. As such, the LC was viewed as unlikely to transmit highly specific information and much more likely to be involved in general behavioral state control (reviewed in Aston-Jones and Cohen, 2005; Aston-Jones and Waterhouse, 2016; Berridge and Waterhouse, 2003; Foote et al., 1983). This view was buttressed by observations of its arousal state-related electrophysiological activity and the slow conduction velocity of its axons.

However, in contrast to these early views, numerous subsequent observations have suggested various degrees of compartmental organization within LC, especially in terms of the origins of LC efferents to particular brain regions (reviewed in Totah et al., this issue). For example,

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Chandler and colleagues (Chandler et al., 2014) have demonstrated that in rat there are distinct LC subpopulations projecting to prefrontal, orbital frontal, anterior cingulate and primary motor cortex (see also Waterhouse, this volume). These subpopulations also differ in terms of their expression of glutamate receptor mRNAs, spontaneous discharge rate, and other electrophysiological properties. Such findings point to possible functional subdivisions in LC that are characterized by specialization along multiple coordinated dimensions.

Further developing this perspective are recent coordinated anatomical, physiological, and behavioral observations by Uematsu and colleagues that provide strong evidence of one example of compartmentalized functional organization within the rat LC (Uematsu et al., 2017; see also a commentary by Seo and Bruchas, 2017). This includes the demonstration that distinct collections of LC neurons project to the amygdala versus the medial prefrontal cortex. Physiological evidence from these studies indicates amygdala projecting LC neurons promote aversive learning while the prefrontal projecting ensemble supports extinction of such learned behaviors. These studies utilized a panoply of methods including cellular recording, selective optogenetic activation and inactivation, anterograde and retrograde tracing, and behavioral methods to elaborate how anatomically distinct LC subpopulations subserve discrete behavioral functions. This strategy could be used in future studies to determine how widespread such intra-LC modularity is across various behavioral dimensions.

However, it is notable that numerous other anatomical studies generally come down on the side of limited modularity. For example, studies by Loughlin and colleagues (Loughlin et al., 1982; Loughlin et al., 1986a; Loughlin et al., 1986b) characterized the LC as being composed of morphologic subtypes of NE-containing neurons that are clustered within sub-regions of the nucleus. These subtype clusters show broad differences in their efferent projections, but there is a core set of cells that projects very widely throughout the neuraxis, with at least some individual cells projecting to functionally diverse cortical areas. More recently, a highly detailed quantitative study of LC afferent-efferent organization in mouse (Schwarz et al., 2015) demonstrates only limited LC modularity. Using viral-genetic techniques, this study provides evidence that there is extensive convergence of multiple, functionally heterogeneous (as far as is known) inputs onto LC neurons in a largely non-topographic manner. In terms of efferent organization, these investigators demonstrated extensive divergence of axons from individual neurons into multiple brain regions (see also, Berridge and Waterhouse, 2003; Espana and Berridge, 2006). They found some examples of sub-nucleus specialization in input-output relations, but the overall picture is one of extensively convergent, non-topographic targeting of afferents, and fairly uniform massive divergence of efferents, with only limited topographical organization. Such observations are an obstacle to schemas that envision LC neurons as receiving and responding to highly specific signals and then transmitting to spatially limited, functionally focused target zones.

The apparent discrepancies among these various anatomical studies may well be due to technical issues, such as tracer efficiency or quantification methods. As such, it is important to interpret the available data cautiously. Going forward, this is clearly a topic that will need to be systematically addressed using the best available methods.

How “smart” is the LC?

Evidence of modularity within the LC and its projections raises questions about the potential functional implications of such organization. Modular organization of afferents and efferents could permit specifically timed and functionally relevant signals to be sent from a module to circumscribed, functionally relevant targets. In this view, the LC would be a “smart” nucleus, with subsets of LC neurons participating actively, selectively and independently in the regulation of diverse forebrain functions.

In the present collection of articles, studies by Totah are provocative in this regard, suggesting that discharge activity varies substantially among LC neurons. Specifically, in anesthetized rat, the majority of simultaneously recorded pairs of LC neurons did not exhibit strictly synchronized activity for either “tonic” spontaneous discharge or foot-shock driven “phasic” discharge. Nonetheless, in some cases, there was correlated activity among distributed ensembles within the nucleus. Moreover, cells within an ensemble tended to have similar efferent forebrain projections as assessed by antidromic activation. Thus, the author proposes that differences in individual and ensemble LC activity could provide signaling to diverse forebrain regions across a variety of time domains. This could allow for LC participation in distinct cognitive/behavioral processes that operate on multiple time-scales. While intriguing, it should be noted that these limited and early-stage observations require further study, documentation and validation, particularly in unanesthetized animals engaged in various behavioral tasks.

Spatial, temporal and functional specialization of discharge activity among LC neurons would largely depend upon corresponding anatomical and physiological specialization of LC afferents. As noted above, some observations do not support the existence of topographic afferent organization. However, as Seo and Bruchas (Seo and Bruchas, 2017) have pointed out, even with a non-topographic distribution of highly convergent afferents to the LC, the transmitter heterogeneity of these afferents offers the possibility of different temporal LC response modes, e.g., tonic or phasic, depending upon which afferent or ensemble of afferents is activated. It will be important to determine whether LC afferents are sufficiently differentiated to drive activity that is specific in terms of sensory modality, timing, task engagement and other dimensions. Some differences in discharge patterns of LC neurons could also be due to intra-LC mechanisms such as gap junctions, recurrent collaterals, inhibitory feedback of released NE, or other effects. There could also be peri-LC interactions between extended LC dendrites and a pool of GABA neurons known to be located just outside the LC (Aston-Jones et al., 2004). Adding to the complexity of LC action, LC-NE axons possess both traditional synaptic release sites, with a closely juxtaposed post-synaptic specialization, and volume/extrasynaptic release sites that are not adjacent to post-synaptic junctions (Bach-y-Rita, 1995; Zoli et al., 1998). The spatial relationship of a release site to post-synaptic receptors likely impacts the extent to which brief, phasic, fluctuations in release are conveyed with high fidelity to these receptors. Thus, functionally-specific actions of distinct patterns of LC discharge activity may be, in part, supported by variations in the spatial relationships between release sites and receptors.

How potent and specialized are LC-NE effects on sensory processing?

The term “modulator” is appropriately applied to NE action within sensory circuitry, as it does not generate sensory signaling *per se* but exerts potent modulatory influences (reviewed in Waterhouse, this issue). We currently lack a full understanding of the extent to which the LC-NE system influences sensory processing under behaviorally relevant conditions. Nonetheless, as reviewed by Devilbiss in this issue, many general features of NE modulation of sensory signaling have been identified in the well-characterized system for rodent vibrissae sensory processing. This work identifies heterogeneous actions of the LC-NE system that are dependent on: 1) the LC firing mode (phasic vs. tonic); 2) the terminal field (thalamus vs. cortex) and 3) individual neurons within a terminal field. To date, much of the prior work regarding LC-NE action on sensory processing has utilized older methodology with associated limitations (i.e. electrical stimulation, pharmacological manipulations). The advent of new methodology for the selective manipulation of LC neurons with high temporal precision, provides great potential for more fully understanding the actions of the LC-NE system in sensory processing. Important questions for future studies include better defining the impact of varying rates of LC discharge across a range of magnitudes and times scales across varying stages of a sensory processing system. A challenge for this work will be disentangling direct actions of NE within a region from indirect actions of NE at other stages of sensory processing or on behavioral state.

Additionally, our understanding of the actions of the LC-NE system on behavioral measures of perception is limited. In a series of elegant studies utilizing optogenetic activation of the LC, Froemke and colleagues report in this issue and elsewhere (Martins and Froemke, 2015) that the sustained pairing of LC activation with auditory stimuli leads to a strengthening of auditory sensory neuron response properties and improvement in perceptual ability. It will be important to adapt this type of approach to determine the impact of acute manipulations of both phasic and tonic LC activity on psychophysical aspects of perception across multiple sensory modalities.

Related to the actions of NE on sensory perception, the Navarra article in this issue reviews observations suggesting that some of the beneficial effects of psychostimulants on performance, for both ADHD and non-ADHD individuals, are mediated by NE enhancement of sensory processing. It is proposed that specific pharmacological potentiation of NE effects on sensory processing represents one approach for improving aspects of behavioral performance.

How does the LC influence behavior?

Current data indicate that the LC-NE system influences behavior in multiple ways. The most fundamental influence may be its participation in the determination of behavioral state. LC activity is strongly correlated across the spectrum of arousal, from intense waking vigilance to drowsiness to REM sleep in which the animal is unresponsive to even moderately intense sensory stimulation, although there is considerable variability in LC activity within the waking state depending on behavioral circumstances (reviewed in Aston-Jones and Cohen, 2005; Aston-Jones and Waterhouse, 2016). It is well documented that LC-NE activation is

sufficient to induce electroencephalographic and behavioral indices of arousal (e.g., see Berridge and Foote, 1991; Berridge and Foote, 1996; Carter et al., 2010). In the context of LC's role in behavioral state control and the possibility of experimentally controlling LC activity, it is intriguing to consider the observation that LC-NE neurons are virtually silent during rapid-eye-movement (REM) sleep (Aston-Jones and Bloom, 1981; Hobson et al., 1975) implying that LC inactivity plays at least a permissive role in REM sleep initiation and/or maintenance. Selective, verifiable methods for controlling LC neuronal activity have begun to enable testing of that hypothesis. Using opto-genetic methods, Carter (Carter et al., 2010) observed that LC stimulation induced sleep-to-wake transitions from both REM and non-REM (NREM) sleep. LC silencing during waking led to shortened wake episodes but did not increase the duration of either NREM or REM episodes. Thus, LC-NE appears to be one component, quite possibly a necessary and sufficient one, of a complex ensemble of ascending activating systems that induce various aspects of arousal (see also Takahashi et al., 2010).

However, perhaps the most significant lacuna in our understanding of the LC-NE system is how its organization, diversity of firing modes, variety of projections and spectrum of modulatory actions across regions and individual neurons combine to influence perceptual, affective and cognitive aspects of behavior within the waking state. There is not yet a comprehensive, explicit, testable theory of such aspects of LC-NE function (see Aston-Jones and Cohen, 2005 for the most comprehensive theory to date). This primarily reflects a lack of the extensive information needed to achieve such a goal. This includes our currently incomplete understanding of the response properties of LC neurons (both tonic and phasic) to varying environmental events and varying contexts as well as the degree to which LC neurons display heterogeneity in response properties. The absence of this information severely limits our ability to fully understand LC function. The small size and compact nature of the nucleus has long presented challenges to obtaining high-quality single unit recordings in behaving animals. Given this, it is critical that robust histological and electrophysiological data are provided in any study to unambiguously document the anatomical specificity and quality of LC recordings. A key issue to be addressed in future studies is whether heterogeneity in LC neuron response properties aligns with heterogeneity in anatomical projections and/or inputs. In short, what is needed is a compendium of well documented physiological recordings from LC neurons during a variety of behavioral circumstances to identify correlations between LC activity and specific behavioral events. Such a database would permit relevant testing of causal relationships with manipulative techniques.

In the past, our ability to test the behavioral actions of the LC was severely limited by the available methodology (e.g., lesions and electrical stimulation). The development of viral vector-based optogenetic and chemogenetic methodology for the selective manipulation of phasic vs. tonic LC firing across varying time frames represents a significant advance in our ability to address this issue. Excellent examples of the use of this newer methodology as applied to understanding the behavioral functions of the LC can be found in Martins and Froemke, 2015 (and Froemke, this issue) and Uematsu et al., 2017. Since LC neurons display a limited range of activity, it is critical that all manipulations are confirmed to elicit changes in firing rate 1) within the desired range; 2) across the desired time frame; and 3)

with the desired firing pattern. While this represents a technical challenge, it is now possible to achieve these goals (see Martins and Froemke, 2015).

It is not currently possible to provide a straightforward characterization of LC-NE function. How should we integrate what we know about the effects of LC-NE across the wide diversity of regions whose functions it impacts? Do the myriad of LC-NE actions constitute temporally coordinated aspects of cohesive brain states and transitions between brain states? Does LC serve an alerting function and then act to maintain an awake state with a normative level of sensory processing across all sensory modalities? Is the influence of LC-NE within the waking state temporally discrete and divided between phasic and tonic modes of LC activity? Does LC-NE trigger specific aspects of behavior or more generally modulate ongoing behavior? In addition to state-characteristic actions, are there state-independent actions that are, to one degree or another, regionally limited and functionally focused? Such specialization could depend on intra-LC mechanisms and on differentiated terminal zone actions to various degrees. The view that LC acts to differentially impact diverse terminal fields contrasts with earlier views of the nucleus as a state-dependent and non-specific modulatory system. It is important to note that these are not mutually exclusive hypotheses. Indeed, the available evidence argues for the LC supporting both general and state-dependent functions upon which are superimposed potentially more finely grained and functionally-specific actions. Much of the specificity of LC-NE participation in forebrain functions could come from its interactions with specialized, localized circuitry upon which it would have highly differentiated effects.

Are LC-NE effects similar across species?

Most existing data on the neuroanatomy and physiology of the LC have come from rat and monkey. These observations, and more limited ones from other species, point to numerous analogies across phylogeny in the anatomy, physiology and postsynaptic effects of the LC-NE system. However, with LC-NE innervating such a large number of brain regions that have undergone such substantive changes across phylogeny, the question arises of how LC-NE influences may have been altered during evolution. For example, the massive development of neocortex in primates appears to have been accompanied by a parallel expansion and regional specialization of NE innervation (reviewed in Foote, 1997). Articles in this issue, and previous data, have pointed to possible reciprocal influences between prefrontal cortex and LC (e.g., Jodo and Aston-Jones, 1997; see also Aston-Jones and Waterhouse, 2016). Primate prefrontal cortex is vastly more developed and elaborate than analogous/homologous regions in rodent. If this neocortical region is influenced by LC-NE and in turn plays a substantial role in influencing LC activity and function, the question is posed of how different that role might be across this large phylogenetic gap. Nonetheless, Arnsten and colleagues have largely observed comparable actions of NE on prefrontal cortex-dependent cognitive function across rat, monkey, and in the context of the pharmacology of ADHD, humans (Arnsten, 2011). The large primate brain poses additional challenges for the long, extensively arborized, slowly conducting LC axons to play a “smart” role in sensory processing. In considering the question of LC/NE impact on sensory processing, it is worth noting major differences between rodent and primate in the NE innervation of sensory pathways. For example, the lateral geniculate nucleus is well

innervated in rat and essentially not innervated in monkey, indicating species differences in the way the LC-NE system projects to and regulates signal processing along the same sensory pathway. Moreover, in monkey there is enhanced density of NE innervation in those visual structures involved in spatial organization compared to those involved in object identification and pattern analysis at the mesencephalic, diencephalic and neocortical levels (Morrison and Foote, 1986; reviewed in Lewis et al., 1987). An interesting possibility is that in rodent there is an analogous specialization and enhancement of LC-NE innervation of the olfactory and whisker related systems that are more important in the sensory control of behavior in these species (see articles by Linster this volume; Devilbiss, this volume). Differences in the density of innervation implies differences in NE release and differential regulation of signal processing along sensory pathways and between sensory modalities. One area of strong similarity between rat and monkey is the LC and subcoeruleus innervation of spinal cord. In both species, this innervation originates from the caudal and ventral portions of LC proper and prominently from the subcoeruleus (Loughlin et al., 1986a; Westlund et al., 1991; reviewed in Foote, 1997). We are not aware of any detailed studies in primate utilizing multiple tracers to examine the issue of heterogeneity in efferent projections among LC neurons. Such studies in rodent have yielded evidence for non-overlapping projections or overlapping projections depending upon the labels used and the sites injected (for reviews see Waterhouse, this issue; Schwarz et al., 2015; Uematsu et al., 2017). Of course, afferent innervation of LC may well also have evolved, but studies in monkey have been too limited to allow comparisons (reviewed in Foote, 1997).

Next steps.

As we have indicated, there are fundamental, high priority issues to be addressed that build upon a large number of interwoven observations. Fortunately, this need coincides with the recent development of an array of sophisticated tools that enable measuring and manipulating various aspect of LC function that can be used to more definitively address these issues.

For example, recent technical advances in measuring neuromodulator release (Patriarchi et al., 2018) offer the promise of determining the relationships among the intensity and timing of NE release in LC terminal fields, LC discharge activity, and specific NE effects in terminal fields on sensory and behavioral processes. This new methodology, which can be used in behaving animals, has sub-second temporal resolution as well as spatial resolution down to the single cell level on the cortical surface. This would permit assessment of the spatial and temporal differentiation of NE release across brain regions and segments of behavior. Such spatio-temporal refinement would permit testing hypotheses regarding the spatial distribution and timing of NE release in response to different stimuli and behavioral conditions. Such studies would address important aspects of major questions posed above. Does NE release occur lockstep across various terminal fields or is there considerable heterogeneity in the timing or behavioral correlates of release? How refined is the spatial and functional resolution of NE release? Are various chronic or acute manipulations of LC activity producing the expected effects on NE release?

It is significant that new anatomical and physiological methods with cellular resolution will now facilitate the testing of hypotheses regarding LC functions, including how it impacts sensory processing to influence the timing, intensity and character of specific behaviors. For example, as noted above, the strategy and techniques used by Uematsu and colleagues (Uematsu et al., 2017) could be adapted to explore other possible behavioral functions of LC and rigorously test multiple functional hypotheses of the LC that have been posited. A major technical challenge is to be able to manipulate LC activity across time scales (e.g., phasic, short tonic, long tonic) in physiologically relevant patterns in order to measure the perceptual/cognitive actions of such activity. The technical challenge is greatest for phasic activity because long trains of activation at phasic rates are not physiologically relevant. Yet, without direct physiological confirmation, it is difficult to know whether a single phasic series of light pulses is sufficient to drive a majority of LC neurons in a physiologically relevant manner. In addition to these technical considerations, a major complication for stimulation studies is that if the LC is as heterogeneous as has been suggested (see above), synchronous activation throughout the nucleus may not be entirely physiologically relevant.

This is an exciting time in neuroscience with many new methods available to rigorously test explicit hypotheses about the functions of specific neural networks (see Koroshetz et al., 2018 for recent examples). The spatial and temporal specificity of these methods have begun to enable experimental tests of hypotheses of LC function with a precision that has not been previously possible. Such testing will hopefully lead to a comprehensive, testable theory of LC-NE function.

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