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"What have we GANEd?" Application of a theoretical construct to explain experimental evidence for noradrenergic regulation of signal processing in sensory networks.

Rachel Navarra[1] and Barry Waterhouse[2]

[1]Department of Pharmacology and Physiology and [2]Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA. 19129
rachel.lynn.navarra@drexel.edu and barry.waterhouse@drexelmed.edu

Abstract: The GANE theory provides a mechanism for amplifying noradrenergic modulatory actions and enhancing the processing of imperative stimuli for immediate action or future experience-guided action. However, the theory requires refinement to account for physiological fluctuations in NE efflux and phenomena associated with noradrenergic regulation of non-imperative sensory signal transfer.

Mather and colleagues have proposed an intriguing theory to explain how norepinephrine (NE) release and subsequent noradrenergic modulatory actions are focused in neural circuits by concomitant "priority" stimulus-driven release of glutamate. In doing so they confront a question that has perplexed the field for some time, i.e. how to account for *selectivity* of signal processing in noradrenergic terminal fields and *focused* perception of salient events when tonic discharge from the broadly projecting NE-containing nucleus locus coeruleus (LC) is elevated, as would occur during generalized arousal. Here we focus on how the theory applies to NE modulation of sensory signal processing. Given the results of four decades of published work we would expect increases in LC-NE output to promote enhanced neuronal and neural network responses to sensory-driven afferent inputs (Berridge and Waterhouse, 2003), actions that have been linked to improved performance of sensory guided behavioral tasks (Aston-Jones *et al.*, 1999). Until recently, the conventional wisdom was that the LC-NE efferent network was broadly distributed from a relatively small number of brainstem neurons with homogeneous physiological properties. Given this, the presumption was that NE was released uniformly and simultaneously across all terminal fields within the forebrain, cerebellum, and spinal cord for as long as LC is discharging, either tonically or phasically. If this were the case,

neuronal and neural circuit responsiveness to sensory driven afferent inputs would be increased throughout the CNS without any bias in favor of one sensory signal vs another. If responsiveness to synaptically-driven inputs is elevated everywhere and for every modality, what has been gained? Is there a way for the LC-NE system to selectively differentiate sensory signals from the constant stream of information that is presented to the nervous system from the periphery? Mather's GANE theory is timely insofar as it appropriately confronts these issues.

An idea similar to the current theory was suggested by Marrocco and colleagues (1987) after they observed a correlation between catecholamine release in monkey visual cortex and coincident light-evoked activity in geniculostriate projections to ocular dominance columns. These authors postulated a local interaction between NE fibers and geniculostriate afferents; one that created a local hot spot for NE release within the visual cortex and thus preferentially promoted modulation of synaptic transmission at this site. Akin Marrocco's proposal, the GANE theory argues that locally released glutamate provides the means for amplifying release of NE from tonically active LC-NE fibers.

The GANE theory accounts for many but not all of the well documented attributes and operational capacities of the LC-NE system, particularly those demonstrated in sensory networks. The authors exhaustively reviewed an extensive literature including many reports that support the core of their proposal – a positive feedback mechanism whereby synaptic release of glutamate amplifies NE release from nearby noradrenergic axons and results in enhanced responsiveness of neurons and glia to glutamate neurotransmission at this local site of interaction. The process relies upon a delicate balance and interplay between receptor mediated actions that are triggered as extracellular concentrations of NE and glutamate change. The temporal and spatial dynamics of these interactions are postulated, but experimental evidence to support the details of these mechanisms is lacking. For example, to date the extracellular tissue concentrations of NE that yield the range of modulatory actions demonstrated in vivo and in vitro have only been crudely approximated. As shown in many studies, LC-NE modulatory effects are expressed according to an inverted-U dose response curve, rising to optimal facilitation of cellular

and behavioral events as LC-NE activity increases and then falling to suppression of neuronal responsiveness and disrupted task performance as NE concentrations and LC discharge increase further (Aston-Jones *et al.*, 1999, Devilbiss and Waterhouse, 2000). At what point along this inverted-U function is the glutamate-NE interaction operating? At some level of glutamate release, the facilitating actions of NE would be expected to diminish along the right side of the function.

Other aspects of LC-NE action require attention in the GANE model. For example, GANE relies on beta receptor mediated modulation of excitatory synaptic transmission and minimizes a role for alpha-1 receptors, despite evidence in sensory circuits that alpha-1 receptor activation augments postsynaptic responses to excitatory inputs (Mouradian *et al.*, 1991, Rogawski and Aghajanian, 1982). In this same vein, beta receptor activation has been shown to enhance postsynaptic responses to GABA (Cheun and Yeh, 1992, Waterhouse *et al.*, 1982). This latter mechanism could account for the enhanced lateral inhibition that is invoked as a means of establishing additional contrast between a priority stimulus-driven hot spot and its tissue surround. Evidence for increased lateral inhibition and focusing the zone of neural excitation created by prioritized inputs can be found in studies that examined the impact of the LC-NE system on off-beam inhibition in the cerebellar cortex (Moises *et al.*, 1983) and receptive field properties of visually responsive neurons (Waterhouse *et al.*, 1990). Finally, a "gating" effect of the LC-NE system on otherwise subthreshold synaptic inputs has been demonstrated in multiple brain circuits (Waterhouse *et al.*, 1988). This action of NE would serve to recruit additional neurons into a sensory response pool as opposed to suppression of hot spot surround activity.

In summary, the model works reasonably well in support of circumstances where a noradrenergically-innervated circuit is called upon to process behaviorally imperative information that should be prioritized for immediate response and/or accentuated for future retrieval and experience-guided action, e.g. fear related or reward generating stimuli. However, it is well to remember that much of the evidence for NE modulatory actions in sensory circuits has been demonstrated in anesthetized or controlled waking

conditions where stimuli are behaviorally irrelevant. How does GANE account for bottom up differentiation and prioritization of sensory signals in the absence of behavioral relevance? We applaud the model, but look forward to resolution of how GANE integrates with conventional NE modulation to differentiate signals amidst the constant stream of incoming information from the sensory surround at both early stage sensory relays and areas of higher order sensory integration.

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