

## **Are there “local hot spots?”: When concepts of cognitive psychology do not fit with physiological results.**

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**Abstract:** Mather et al.’s arguments in the target article need rethinking at the mechanistic levels. The arguments on the physiological effects of NE at the cortical level are inconsistent with large parts of the literature. There is no evidence that NE induces local “hot spots”: NE mainly decreases evoked responses, facilitating effects are rare and not localized. More generally, the idea that perception benefits from “local hot spots” is hardly compatible with the fact that neural representations involve largely distributed activation of cortical and subcortical networks.

Mather and colleagues propose that phasic activation of LC neurons biases perception and memory. They suggest that elevated levels of glutamate at the site of prioritized representations increase local NE release, creating “NE hot spots.” At these spots, enhancement of glutamate and NE release mutually enhance and amplify the activation of prioritized representations. This excitatory effect contrasts with widespread NE suppression of weaker representations via lateral and auto-inhibitory processes.

The authors describe a schema at the cellular level (figure 6), but is it supported by physiological data obtained in sensory cortices? The Locus Coeruleus (LC) neurons project widely to many cortical areas, although recent data indicate that some neurons project more to a particular area (the prefrontal or the motor cortex) than others (Chandler et al. 2013; 2014). Within an area, NE is released in the extracellular space from NE

varicosities and reach the entire cortical network. When sensory stimuli are processed by cortical neurons, glutamate is released by the thalamo-cortical terminals. How does NE affect the cortical processing? Iontophoretic application of NE performed in the somatosensory, visual and auditory cortices revealed that, in most of the cases, NE depresses evoked responses (e.g. Videen et al. 1984; Kolta et al. 1987; Manunta & Edeline 1997; 1998), an effect replicated in awake animals (Foote et al., 1975; Bassant et al., 1990; Manunta & Edeline, 1999). Moreover, in awake rats tonic activation of LC neurons by continuous low frequency stimulation (1Hz) triggered similar effects: decreased evoked responses in 63% of cells in the rat somatosensory cortex (Devilbiss & Waterhouse 2004). It has been argued that these inhibitory effects were a consequence of too high concentrations of NE at the vicinity of the cell (Waterhouse et al., 1998a), but this seems unlikely given that pronounced depression of evoked responses were also observed with very low ejection currents (Manunta & Edeline 1997; Ego-Stengel et al., 2002; review in Edeline 2012). If the hot-spot theory was the main mechanism at play, then exogenous application of NA would more likely increase evoked activity.

But what are the consequences on the neurons' functional properties? In auditory cortex, the suppressive effect of NE promotes an increase in frequency selectivity both in anesthetized and unanesthetized animals (Edeline, 1995; Manunta & Edeline, 1997; 1999). In the visual cortex, application of NE improved the velocity and direction selectivity of cells, without modifying the orientation selectivity (McLean & Waterhouse, 1994; Ego-Stengel et al., 2002). These results clearly point out that the effects of NE (and other neuromodulators) can differ depending on the stimulus dimension. For example, a dimension that depends on thalamo-cortical afferences (such as frequency tuning in the auditory cortex, or size of the receptive field in the visual cortex) could be more affected than a dimension that relies more on cortico-cortical afferences (such as frequency modulation tuning in the auditory cortex, or velocity tuning in the visual cortex). Yet, glutamate is released in all cases, showing that the glutamate/norepinephrine interaction is not as straightforward as described by the authors.

One may ask is it possible that "NE hot spots" emerge when NE is repeatedly associated

with glutamate release at particular synapses? When a stimulus, which activates a specific set of synapses, is paired with phasic LC stimulation, a predominant decrease in neuronal activity is initially reported in several cortical areas (Olpe et al., 1980; Sato et al., 1989). However, in the somatosensory cortex, both the excitatory and the inhibitory components of evoked responses are facilitated when phasic stimulation of the LC is delivered before tactile stimuli (Waterhouse et al 1998b; Snow et al 1999). In fact, in several sensory modalities, LC stimulation rather impacts on the temporal organization of evoked responses (Bouret & Sara 2002), by shortened evoked responses and reducing the first spike latency and its variance (Lecas 2001, 2004). In the auditory cortex, facilitation of evoked responses is the dominant effect when stimulation of the LC is delivered before a particular sound frequency (Edeline et al. 2011; Martins & Froemke 2015), which contrast with the dominant depressive effect obtained when phasic pulses (1sec) of NE are iontophoretically delivered in the vicinity of the recorded cells (Manunta & Edeline, 2004). In fact, via its projections onto other brain nuclei, LC stimulation activates other neuromodulatory systems such as the cholinergic (Berridge et al 1991, 1993) and the serotonergic (Kim et al. 2004) systems. The difference between the effects obtained with iontophoretic application of NE and LC stimulation points to other neuromodulators likely contributing to the effects observed at the cortical level.

Mather et al also suggested that local “NE hot spots” bias perception. But is there any evidence that NE facilitates the discrimination performance of cortical neurons? When the responses of cortical neurons are tested with a set of conspecific and heterospecific vocalizations having the same spectral content (thereby activating the same sets of synapses), NE application induces either an increase or a decrease of the response, and, on average discrimination of overall performance of cortical neurons is unaffected. However, a small population of neurons displaying the largest increase in responses exhibit enhanced discrimination (quantified by the mutual information) between communication sounds (Gaucher & Edeline, 2015). This population of neurons corresponds to recordings showing smaller receptive fields; they are not located in a particular layer and are distributed across the whole cortical map. As for any natural stimulus, representations of these vocalizations are distributed among largely overlapping

cortical and subcortical networks. Therefore having local “NE hot spots” in such networks will not help perceiving such stimuli. Subtle, and transient, synchronizations between distributed populations of neurons are potentially more relevant for discriminating natural stimuli.

To conclude, based on physiological results from sensory cortices, it is clear that the dominant effect of NE is widespread suppression of excitatory inputs both when responses are tested with artificial and natural stimuli. NE promotes facilitated responses for only a small proportion of cells; this effect is more common with LC activation probably because of activation of other neuromodulatory systems. Only a small fraction of these facilitated responses displayed enhanced discriminative performance. Therefore, the view of local "NE hot spots" theory receives little support from current physiological results. Although we cannot dismiss the ‘hotspot theory’ might account for certain specific forms of perceptual alterations, we believe this theory is inappropriate to account for facilitations of perceptive abilities. It remains to be demonstrated that local interactions between NE and Glutamate promote enhanced perceptive abilities, particularly due to the inherent distributed representation of any natural stimuli.

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