Commentary on Mather, M., Clewett, D., Sakaki, M., & Harley, C.W. (in press). Norepinephrine ignites local hot spots of neuronal excitation: How arousal amplifies selectivity in perception and memory. Behavioral and Brain Sciences.

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Amplified selectivity in cognitive processing implements the neural gain model of norepinephrine function

Authors: Eran Eldar[1,2] e.eldar@ucl.ac.uk
sites.google.com/site/eldareran/
Jonathan D. Cohen[3,4] jdc@princeton.edu
www.csbmb.princeton.edu/ncc/
Yael Niv[3,4] yael@princeton.edu www.princeton.edu/~nivlab/

[1] Wellcome Trust Centre for Neuroimaging, University College London, London WC1N 3BG, UK, Tel: +44 (0)20 3448 4362
[2] Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London WC1B 5EH, UK
[3] Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08544, Tel: 609 258 0826
[4] Psychology Department, Princeton University, Princeton, NJ 08544, Tel: 609 258 4442

Abstract: Previous work has suggested that an interaction between local selective (e.g., glutamatergic) excitation and global gain modulation (via norepinephrine) amplifies selectivity in information processing. Mather et al. extend this existing theory by suggesting that localized gain modulation may further mediate this effect — an interesting prospect that invites new theoretical and experimental work.

Mather at al.'s article joins the growing body of work suggesting that norepinephrine, through its brain-wide effect on neural gain, selectively enhances useful and salient neural representations (Usher et al. 1999; Aston-Jones & Cohen 2005; Eldar et al. 2013). Building on an early computational model of catecholamine function (Servan-Schreiber et al. 1990), and later work directly addressing locus coeruleus function (Usher et al. 1999), Aston-Jones and Cohen (2005) proposed that one of the roles of the locus coeruleus–norepinephrine system is to enhance, through gain modulation, neural representations that are most useful for maximizing utility ('The Adaptive Gain Theory'). Critically, although norepinephrine is released globally throughout the brain, it was argued that its effects could be temporally and spatially specific. Temporally specific, because norepinephrine can be phasically released in response to task-relevant stimuli, and thus suitably timed to enhance representations that are most useful for task performance. Spatially specific, because gain modulation inherently entails an interaction

between norepinephrine and glutamate in which strong neural representations (i.e., those that are already receiving strong glutamatergic input, due either to "bottom-up" sensory inputs and/or "top-down" context or control) are enhanced by norepinephrine, while weak neural representations are more inhibited (Eldar et al. 2013; Eldar 2014; see also Figure 5 in Mather et al.).

We conducted a series of behavioral and neuroimaging experiments to test this idea, that norepinephrine amplifies selectivity in information processing (Eldar 2014). Specifically, we investigated the relationship between selectivity and pupillometric indices of norepinephrine function in the domains of learning, perception and memory. We first showed that indices of high norepinephrine function are associated with learning that is more selectively focused on stimulus features to which individuals are predisposed to attend (Eldar et al. 2013). We then showed that a similar effect is evident in the domain of perception. Specifically, we found that indices of high norepinephrine function are associated with perception of ambiguous characters that is more selectively focused either on the character's visual features or on its semantic context, depending on which source of information has stronger influence (we manipulated source's strength using subliminal priming; Eldar et al., in revision; Eldar 2014). Notably, this latter finding suggests that norepinephrine will enhance bottom-up (e.g., visual features) or top-down (e.g., semantic) influences on perception, whichever one is stronger. Finally, we also showed that a similar effect is evident in the domain of memory, where we found that indices of high norepinephrine function are associated with recognition memory that is more selective to the font at which a word appears, when attention is drawn to the font by the experimental task (Eldar et al., in revision; Eldar 2014). These findings of increased selectivity in learning, perception and memory were predicted by neural network models of norepinephrine function, in which the effect of norepinephrine was modeled as a global increase in gain.

In addition to the behavioral predictions, our neural network models generated several neural predictions, which we tested using functional magnetic resonance imaging. First, increased gain entails that neural activity should be driven to maximal and minimal

levels, and thus the absolute deviation of activity levels from the mean activity should increase with gain. Second, stronger responsivity to input signals should increase functional connectivity between neural units. Third, functional connectivity between neural units should become more selectively localized in clusters (i.e., less globally distributed), mirroring the behavioral selectivity that is associated with high gain. Indeed, pupillary indices of high norepinephrine function were associated with all three effects throughout the brain, as measured by brain-wide Blood-Oxygen-Level-Dependent (BOLD) signals, further supporting the role of norepinephrine in global gain modulation in humans (Eldar et al. 2013).

The gain-modulation model of norepinephrine function was originally inspired by findings that norepinephrine enhances single-neuron responses to both excitatory and inhibitory signals (e.g., Moises et al. 1979; Waterhouse & Woodward 1980), which suggested that norepinephrine increases the contrast between strongly and weakly active neurons. However, subsequent single-neuron electrophysiology studies showed that norepinephrine may either enhance or suppress responsivity to excitatory input, depending on which receptor it acts on (e.g., Devilbiss & Waterhouse 2000). Mather et al.'s proposal of local positive-feedback interaction between norepinephrine and glutamate reconciles this latter evidence with the neural gain model of norepinephrine function, since it suggests a mechanism through which the gain-enhancing effect of norepinephrine would dominate specifically in strongly activated neurons, and thus, norepinephrine's overall effect would be to increase the contrast between weakly and strongly active neurons, as in the original model (shown in Figure 5 in Mather et al.). In addition, the local changes in norepinephrine that Mather et al. propose may have additional effects that go beyond those of the interaction between local excitation and global gain modulation. For instance, local enhancement of gain may amplify selectivity even further. Indeed, such local changes have been suggested by early *in vivo* studies of the influence of sensory and thalamic inputs on cortical release of norepinephrine (e.g., Marrocco et al. 1987).

In sum, the neural gain model of norepinephrine function has been successful in predicting a range of norepinephrine's neural and behavioral effects, among which is amplified selectivity in perception and memory. Mather et al.'s proposal of local glutamate-norepinephrine interaction further supports the neural gain model, suggesting that additional local interactions may enhance this effect. This suggestion invites further modeling to generate quantitative predictions, and experimental work to test them.

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