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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Does arousal enhance apical amplification and disamplification?

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Abstract: We summarize evidence that input to the apical tufts of neocortical pyramidal cells modulates their response to basal input. As this apical amplification and disamplification provide intracortical mechanisms for prioritization, Mather et al's arguments imply that their effects are enhanced by noradrenergic arousal. Though likely, this has not yet been adequately studied. The target article shows that it should be.

Mather et al argue that as arousal increases things of high priority are perceived and remembered even better, while things of low priority are suppressed even more. Intracortical mechanisms for prioritization of selected signals are a prerequisite for this because the noradrenergic system provides only diffuse low-bandwidth innervation of neocortex, whereas the particular signals to be amplified or suppressed must be specified by locally specific interactions of high bandwidth. We therefore outline recent evidence for intracellular and microcircuit mechanisms by which signals are either amplified or suppressed within neocortex, prior to their further modulation by the noradrenergic system. We refer to those mechanisms as apical amplification (AA) and disamplification. Evidence for AA is provided by patch-clamping studies showing that inputs to the apical tufts of pyramidal cells are integrated separately from inputs to their basal dendrites before being used to modulate the cell's response. Current models of neocortex, including noradrenergic effects, typically assume that pyramidal cells can be adequately thought of us point processors that simply sum all of their excitatory and inhibitory inputs and fire when that sum exceeds a threshold. The evidence for AA shows that some pyramidal cells have not one but two main sites of integration such that, when apical and basal inputs coincide, intracellular calcium spikes initiated by a site of integration near the top of the apical dendrite amplify the cell's response to its basal inputs (Larkum, Zhu, and

Sakmann, 1999; Larkum, et al, 2007; Larkum et al, 2009; Larkum, 2013). The most studied mechanism by which AA is implemented in layer 5 cells is referred to as back-propagation activated calcium spike firing (BAC firing). In addition to these two main integration sites local integration takes place within both basal and tuft dendrites by the regenerative activation of NMDA receptors (NMDA-spikes). AA may be fully implemented by NMDA-spikes alone in supragranular neurons (Palmer, 2012), but even in subgranular neurons, NMDA-spikes have an important influence (Larkum et al., 2009). Essential properties of these mechanisms are illustrated in Fig. 1. Inhibitory interneurons that specifically target apical dendrites in layer 1, such as Martinotti cells, produce disamplification, which suppresses amplification without inhibiting action-potential output.

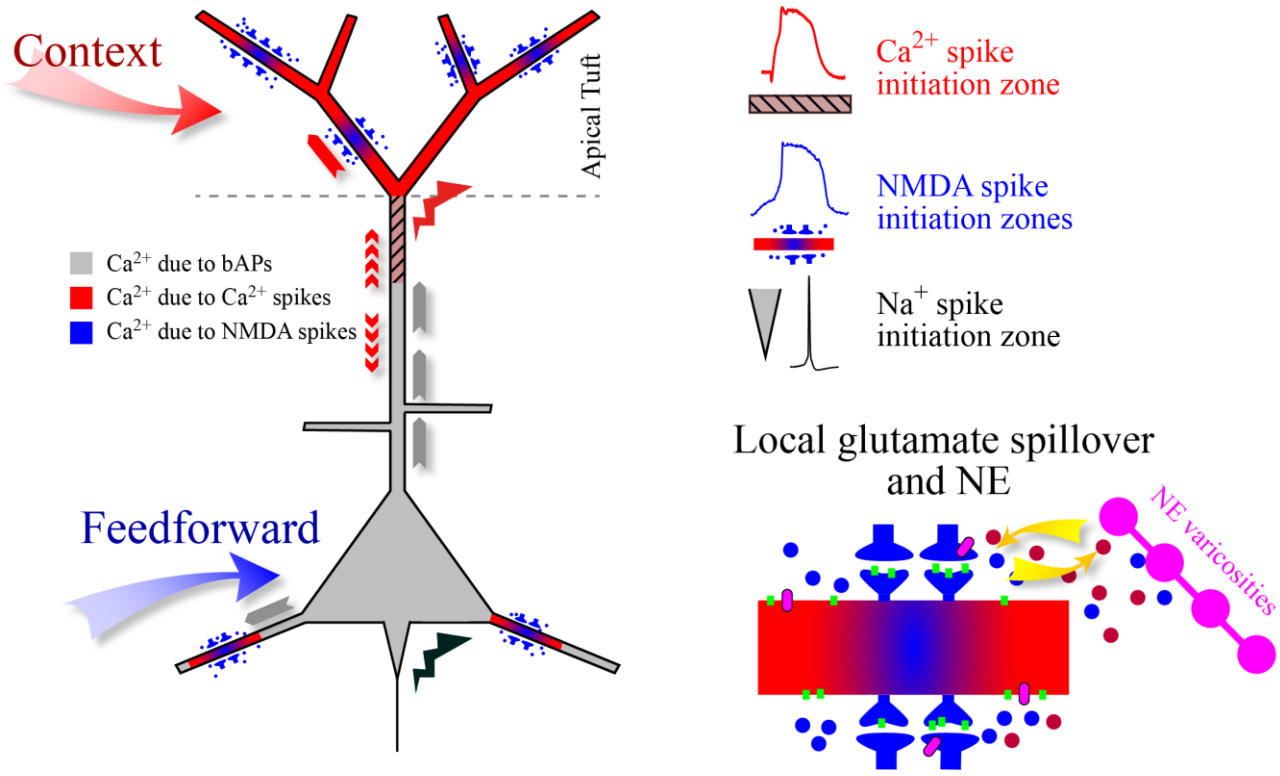

Figure 1. Dendritic spikes in neocortical pyramidal neurons. Apical tufts of pyramidal neurons receive inputs from diverse sources. Calcium currents, and thus synaptic plasticity, depend upon backpropagating action potentials (bAPs, grey), apical dendritic calcium spikes (red) and NMDA spikes (blue). NMDA spikes require both local depolarization and glutamate (blue dots) and are enhanced by glutamate spillover to extrasynaptic NMDA receptors (green squares). Norepinephrine (maroon dots) interacts with glutamate in a feedback process hypothesized to enhance postsynaptic excitability.

Though much of this work has been carried out in vitro, there are strong grounds for supposing that AA and disamplification apply to awake behaving humans (Phillips, et al., 2015). Imaging studies of local dendritic NMDA-spikes in awake behaving animals show the importance of such integrative intracellular processes in vivo (Lavzin et al., 2012; Xu et al, 2012; Smith et al., 2013; Gabino et al., 2014; Palmer et al., 2014; Grienberger et al., 2014; Cichon & Gan, 2014). These discoveries are well-known to cellular neurophysiologists, but not yet to psychologists or cognitive neuroscientists. For a clear introduction to AA and disamplification and their relevance to cognitive function and theoretical neuroscience see Phillips (2015).

Arousal releases norepinephrine (NE), i.e. noradrenalin, which regulates the firing mode of layer 5 neurons (Wang and McCormick, 1993). Many new questions are raised by the possibility of interactions between AA and NE release in these and other neocortical neurons. First, are the effects of NE and AA synergistic, or do they simply sum in some quasi-linear way? Synergistic interactions between AA and mechanisms proposed in the GANE model seem likely because glutamate spillover will not spread from apical to basal dendrites. Spillover is intrinsic to the GANE model because of the non-synaptic component of NE release, and that implicates NMDA more than AMPA receptors. Local dendritic NMDA-spikes are also enhanced by glutamate spillover (Chalifoux and Carter, 2011). To see the possibility of synergistic interactions consider the case to which AA is most applicable, i.e. where apical input is strong and basal input is present but weak. There would then be NE-dependent enhancement of depolarization in the apical tuft but

not in the basal dendrites. That would increase the effect of AA on cellular output while maintaining the need for basal input to initiate axonal spiking. Second, how are NE-receptor subtypes distributed across regions, layers and subcellular compartments, and is that compatible with the modulatory role proposed for tuft inputs? An explicit focus on intracellular and microcircuit mechanisms in theories of arousal requires answers to these questions. Third, will studies of interactions between AA and NE cast light on the putative role of AA in regulating states or levels of consciousness (Bachmann and Hudetz, 2014; Meyer, 2015, Phillips, 2015)? It seems likely that they will. Fourth, do previous studies under-estimate the extent of AA because they do not ensure appropriate levels of noradrenergic input? This is clearly relevant to in vitro studies or under anesthesia, but, Mather et al's hypotheses imply that local phasic arousal needs to be considered as well as tonic arousal when studying awake behaving animals. Finally, are working memory capabilities dependent upon specialized interactions between NE and AA in dorso-lateral PFC (Arnsten, et al, 2012)?

Much intracellular, electrophysiological, cognitive, and computational research is required to answer such questions. If that shows noradrenergic enhancement of AA and disamplification, then that will strengthen and broaden both the GANE model and our understanding of the role of intracellular computations in mental life. If not, then we will need to discover why not. Thus the target article opens the door to a wide array of issues concerning interactions between noradrenergic arousal and prioritization within the neocortex by AA and disamplification. These issues may well be crucial to our understanding of relations between brain and behavior.

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