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.
BBS-D-15-00875_ Mather_ Becchetti & Amadeo

Does the Glutamate Amplifies Noradrenergic Effects (GANE) model help explain why we fail to remember our dreams? Acetylcholine and norepinephrine balance in wakefulness and rapid-eye-movement (REM) sleep.

Andrea Becchetti[1] and Alida Amadeo[2].

[1] Department of Biotechnology and Biosciences and Center for Neuroscience of Milan, University of Milano-Bicocca, 20128 Milano, Italy.
andrea.becchetti@unimib.it
http://www.btbs.unimib.it
Tel: +39-02-64483301

[2] Department of Biosciences, University of Milano, 20133 Milano, Italy.
alida.amadeo@unimi.it
http://www.dbs.unimi.it

Abstract: The ascending fibers releasing norepinephrine (NE) and acetylcholine (ACh) are highly active during wakefulness. In contrast, during REM sleep, the neocortical tone is mainly sustained by ACh. By comparing the different physiological features of the NE and ACh systems in the light of the GANE model, we suggest how to interpret some functional differences between waking and REM sleep.

Regulation of neocortical circuits by ascending regulatory systems involves all of the classic neurotransmitters. Most of the nuclei located in brainstem, hypothalamus and basal forebrain are not only reciprocally connected, but send direct projections to the neocortex (Steriade & McCarley 2005; Saper et al. 2010; Jones 2011). The same applies to the hypothalamic nuclei releasing neuropeptides such as orexin/hypocretin (in wakefulness) and melanin concentrating hormone, MCH (in REM sleep; Jones & Hassani 2008; Monti et al. 2013; Aracri et al. 2013, and references therein). As a first approximation, these bewildering intricacies can be simplified by focusing on the balance between the activity of noradrenergic and cholinergic nuclei, which are crucial regulators of arousal and cognition (e.g., Constantinople & Bruno 2011; Schmidt et al. 2013). Both project varicose fibers that widely innervate the neocortex, and their global effects are excitatory. During wakefulness, high levels of NE and ACh cooperate in regulating

arousal and cognitive processes. However, although cholinergic transmission is certainly implicated in synaptic plasticity (e.g., Berg 2011), the physiological action of NE is thought to be more persistent and more closely related to memory retention and consolidation (e.g., Constantinople & Bruno, 2011; McGaugh 2013; Schmidt et al. 2013). The activity of noradrenergic and cholinergic neurons decreases during non-REM (NREM) sleep, whereas in REM sleep ACh release increases again, while NE activity remains low (Lee et al. 2005; Datta 2010; Saper et al. 2010; Takahashi et al. 2010; **Figure 1**). The fact that neocortex activation in REM sleep is mainly sustained by ACh is a further indication that the cholinergic tone is more directly related to consciousness and executive functions. In fact, the role of REM sleep in memory consolidation remains controversial (Rasch & Born 2013; Ackermann & Rasch 2014).

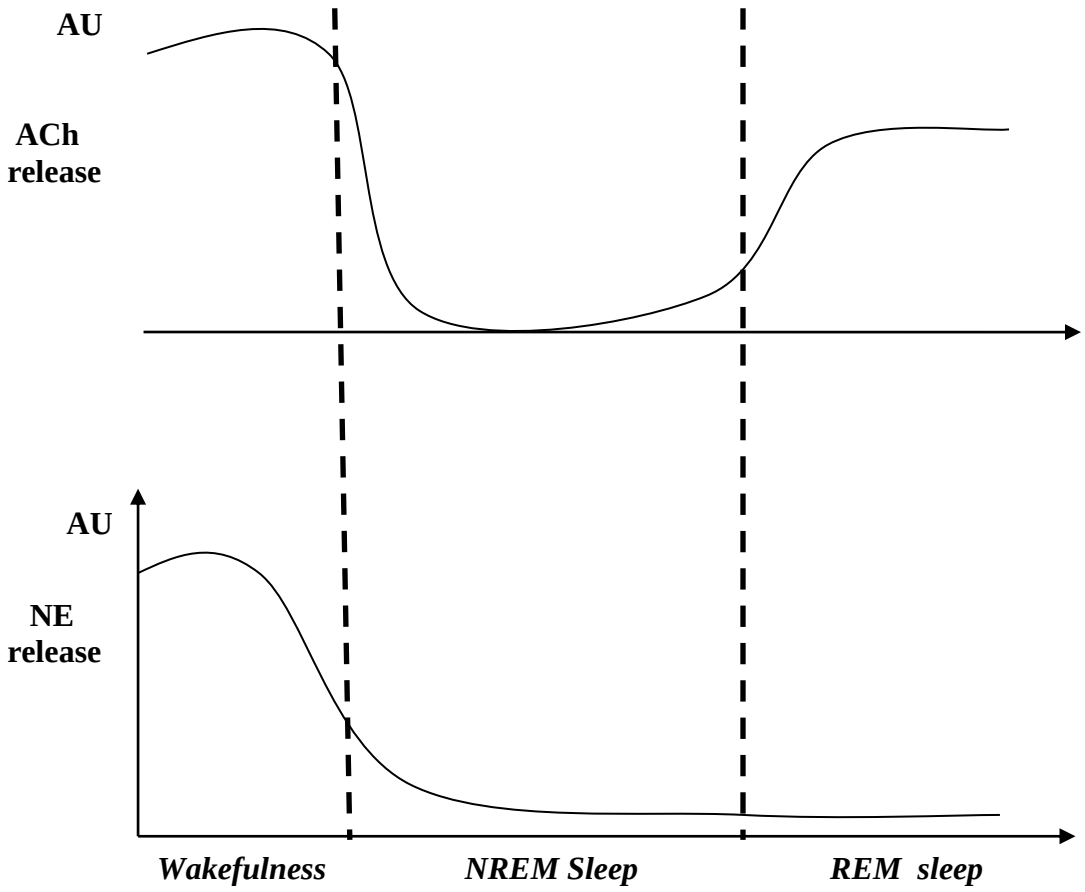

Figure 1. Cholinergic and noradrenergic activity through the sleep-wake cycle. The scheme provides a qualitative comparison of the activity of the ascending cholinergic and noradrenergic projections, with no pretension of quantitative precision.
AU = Arbitrary Units.

Does the GANE model help to suggest possible explanations of the different functional consequences of activating these regulatory systems during brain states? A first central assumption is that, under strong neuronal activation, spillover glutamate stimulates nearby NE varicosities in an NMDA receptor-mediated way. By activating low-affinity β-adrenoreceptors, high NE release would stimulate neuronal excitability as well as glutamatergic terminals, thus constituting activity 'hot spots' that effectively amplify inputs with high priority under phasic arousal. Are such hot spots possible in the cholinergic system? Not much is known about the glutamatergic regulation of ACh

release, but evidence does exist about ionotropic glutamate receptors regulating cholinergic terminals in the neocortex (Ghersi et al. 2003; Parikh et al. 2010). Hence, it is conceivable that spillover glutamate also stimulates cholinergic fibers. Because ACh is well known to increase glutamate release (Marchi & Grilli 2010), a positive feedback loop could generate local ACh hot spots, analogous to those hypothesized by Mather and colleagues.

A second central tenet of the GANE model is that the low threshold α2-adrenoreceptors, by responding to low and intermediate diffuse NE concentrations, would inhibit glutamate release in pathways implicated in low priority signaling, under aroused conditions. Under this respect, the cholinergic system presents several differences compared to the noradrenergic. In particular: i) cholinergic fibers form both well differentiated point-to-point synapses and axon varicosities that sustain more diffuse ACh release (Dani & Bertrand 2007); ii) ACh activates both metabotropic (muscarinic, mAChRs) and ionotropic (nicotinic, nAChR) receptors. In prefrontal regions, M1 mAChRs are widespread and produce excitatory effects related to working memory through different cellular mechanisms (e.g., McCormick & Prince 1986; Gulledge et al. 2009; Proulx et al. 2014). Their EC_{50} for ACh is in the low μM range. On the other hand, nAChRs can be broadly divided into two functional classes (Dani & Bertrand 2007). Heteromeric nAChRs have high affinity for ACh (with EC_{50} in the μM range), relatively low permeability to Ca^{2+} (P_{Ca}) and slow desensitization in the presence of agonist. Homomeric nAChRs have high P_{Ca} (in the order of the one displayed by NMDA receptors), but low affinity for ACh ($EC_{50} \approx 200$ μM), and quick desensitization kinetics. The role of different nAChR subtypes in regulating excitatory and inhibitory transmission is still matter of debate. Nonetheless, a striking difference with NE transmission is immediately apparent. The long-term effects on synaptic consolidation are generally thought to depend on Ca^{2+} signals. However, within the putative ACh hot spots, the efficacy of high-P_{Ca} homomeric receptors would be blunted by quick desensitization. High ACh concentrations would also tend to desensitize heteromeric nAChRs. This would prevent sustained Ca^{2+} entry through nAChRs as well as by nAChR-dependent activation of glutamate release, and thus of NMDA receptors. Therefore, differently from

the case of NE, it seems unlikely that ACh hot spots can produce long-term cellular effects considerably different from those produced by lower ACh concentrations, as mediated by mAChRs and heteromeric nAChRs. On the other hand, stimulation of ACh receptors could contribute to sustain local NE hot spots because of the potentiating effect on glutamate release, when both cholinergic and NE systems are active (a point worth of further study).

In summary, by following up the GANE model reasoning, one is led to conclude that low and high concentrations of NE and ACh produce distinct functional effects on neocortical networks. Low to moderate ACh release sustains global neocortex arousal in both wakefulness and REM sleep. However, in the absence of NE activity (as in REM sleep), cholinergic activity is unable to yield long-term synaptic changes, such as those implicated in memory retention, which would partly explain the well known difficulty of recalling oneiric activity. Instead, high levels of ACh seem more fit to shape the rapid synaptic responses implicated in executive functions, as the quick kinetics of the low affinity nAChRs would suggest. We believe that deeper functional studies of the interplay between the ascending regulatory systems, led by heuristic models such as the GANE, will greatly help progress in understanding the physiological basis of cognition.

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