Brain-wide gain modulation: the rich get richer

Tobias H Donner & Sander Nieuwenhuis

A study now shows how brain-wide gain modulation, indexed by pupil diameter, shapes the structure of brain-wide neural interactions and, consequently, trial-and-error learning.

Just as the gain button on a stereo serves to amplify audio signals, neural gain serves to amplify neural communication. When gain is increased, excited neurons become even more active and inhibited neurons become even less active[1]. That is, an increase in gain increases the contrast of the pattern of activity in a neural network. Gain modulation is a major effect of brainstem neuromodulatory systems, such as the locus coeruleus norepinephrine system, which send diffuse projections to large parts of the brain[1–3]. How does brain-wide gain modulation shape the structure of large-scale neural interactions (that is, functional brain networks[4,5]) and cognitive processing? In their study, Eldar *et al.*[6] noninvasively assessed neuromodulator release and various indices of brain networks in humans, and found that neuromodulation boosts dominant neural pathways and, consequently, the effect of people's attentional predispositions on their trial-and-error learning.

Eldar *et al.*[6] focused on a specific problem in everyday cognition: how does global gain affect trial-and-error learning of associations between stimulus features and reward? When acting in a complex, multidimensional environment, some of us attend to, and consequently learn most about, concrete sensory details, whereas others learn more about abstract semantic concepts (**Fig. 1a**). Such individual attentional predispositions may be a result of prepotent pathways in the sensory-motor networks of the cerebral cortex (**Fig. 1b**). But what if a prepotent dimension and a competing, less strongly represented dimension both contain valuable information? Eldar *et al.*[6] hypothesized that when gain is high, the pre-existing asymmetry between these two networks is boosted. Consequently, attention and learning will be more biased toward one's individual predisposition than when gain is low. Neural network simulations supported these hypotheses.

To address such hypotheses, the authors required a measure of gain modulation in the human brain. Recent studies have suggested that, during constant illumination, the diameter of one's pupil provides a noninvasive proxy for norepinephrine release by the locus coeruleus and, consequently, for neural gain[2,7,8]. This assumption is consistent with the traditional view that phasic changes in pupil diameter during cognitive tasks reflect central arousal[9]. The assumption builds on a close correlation between the activity of locus coeruleus neurons and fluctuations of pupil diameter that has been observed in monkeys[2] (**Fig. 1b**). Furthermore, slow changes in tonic locus coeruleus activity and pupil diameter are commonly inversely related to the magnitude of phasic locus coeruleus responses and pupil dilations during cognitive tasks[2,10]. These insights motivated Eldar *et al.*[6] to use the magnitude of the average task-related pupil dilation as an inverse estimate of each

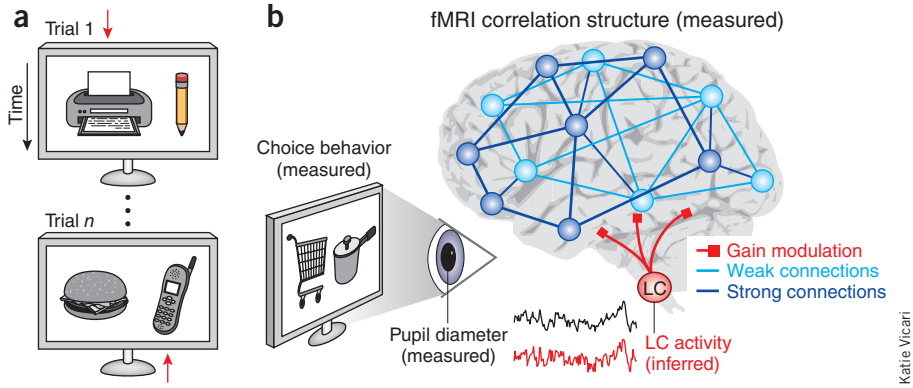

Figure 1 Task design and experimental approach. (**a**) The visual versus semantic learning task. On each trial, participants had to choose one of two objects presented. In each block of trials, one visual feature and one semantic feature predicted reward. Shown are two example trials from a block in which a choice of grayscale images (visual) or office-related objects (semantic) was rewarded (highlighted by the red arrows for illustration only). A choice of colored images or food items did not lead to reward. In most trials, objects differed on either the visual or the semantic dimension, but not both, allowing the researchers to dissociate learning of the reward-predictive feature in each dimension. Participants had to figure out by trial and error how to maximize their total reward. Objects were presented against a gray background, shown in white here for clarity. (**b**) The experimental approach. Choice behavior, brain-wide fMRI correlation structure and pupil diameter were measured and correlated. The black and gray large-scale networks represent strong (prepotent) and weak processing pathways, respectively. Eldar *et al.*[6] propose that this pre-existing asymmetry in the strength of interactions determines learning style and is boosted by locus coeruleus (LC)-mediated global gain modulation. The red lines represent diffuse projections from the locus coeruleus to the forebrain, which modulate neural interactions in both networks depicted. Locus coeruleus activity is inferred on the basis of its correlation with pupil diameter.

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participant's tonic level of neural gain. The researchers expected that this index of neural gain would predict the degree to which an individual's learning performance was dependent on attentional predisposition.

Eldar *et al.*[6] asked their participants to choose between pairs of objects that differed on a visual dimension and/or a semantic dimension (**Fig. 1a**). Participants could gather rewards by figuring out, using trial-and-error learning, which visual feature and semantic feature were associated with reward. The researchers also administered a questionnaire that assessed the extent to which participants were predisposed to process and learn about either sensory (for example, visual) or abstract (for example, semantic) data. They found that the smaller the participants' evoked pupil responses (that is, the higher their inferred neural gain), the more participants' task performance conformed to their learning style predisposition: their choices were more strongly guided by the reward-predictive feature in either the semantic or the visual dimension. These behavioral results were replicated in a separate group of participants in a subsequent functional magnetic resonance imaging (fMRI) experiment.

Network simulations by Eldar *et al.*[6] not only provided mechanistic insights into how a link between tonic gain and learning style may emerge in simple networks, they also yielded two predictions for how global gain changes should affect brain-wide neural interactions (**Fig. 1b**). First, because gain amplifies neural interactions, increases in gain should boost the strong temporal correlations between the activities of local groups of neurons. Crucially, because gain amplifies both excitatory and inhibitory interactions, enhanced gain should boost all strong correlations, regardless of whether these are positive (reflecting excitation) or negative (reflecting inhibition). Consistent with this prediction, the authors observed that the strength of correlations between fMRI voxel time series in various brain regions tracked slow fluctuations in each participant's pupil size: fMRI correlations were strong when baseline pupil diameter was large (that is, tonic gain was high).

The second prediction, based on simulations of a randomly connected recurrent neural network with 1,000 units, was that gain should modulate not only the strength but also the topology of neural interactions: interactions should become more tightly clustered under high gain. If the nearest neighbors of a node in a neural network are also directly connected (that is, correlated above a certain threshold), they are said to form a cluster; the degree of clustering in a matrix of neural correlations can be quantified by means of a clustering coefficient[4]. Again, in qualitative agreement with the predictions, Eldar *et al.*[6] found that the clustering coefficient in the measured network of temporal correlations between fMRI voxels increased with slow increases in pupil diameter (tonic gain). Furthermore, increases in neural clustering predicted a shift in learning performance toward the feature to which each individual was predisposed to attend.

Taken together, the findings of Eldar *et al.*[6] are remarkably consistent with a set of specific model predictions. However, their conclusions about the effects of brain-wide gain modulation are remote from the measurements. Thus, the conclusions rely on several critical assumptions, which future studies will have to verify. For example, it remains to be seen how exactly changes in neuromodulation translate into fMRI measures of neural activity[10]. Given its close link to cellular metabolism, the fMRI signal might be expected to increase coherently throughout the brain under global neuromodulation—a very different pattern from the joint decreases and increases observed for the neural outputs in the simulations. Another assumption is that pupil diameter indexes central norepinephrine release. Although this assumption is attractive, direct experimental support is sparse. High-resolution fMRI may eventually enable more direct monitoring of human locus coeruleus activity concurrently with cortical network dynamics. More specifically, it remains to be verified that individual differences in task-related pupil dilations are inversely related to individual differences in baseline central norepinephrine release (in other words, tonic gain as an individual trait).

One important implication of the study by Eldar *et al.*[6] is that it provides a mechanistic account of how arousal systems can exert selective effects on cognition. Arousal has traditionally been regarded as nonspecific, in sharp contrast to selective attention. This conceptualization is based on the anatomically diffuse organization of the neuromodulatory brainstem systems mediating arousal[2,11]. However, recent advances have made clear that neuromodulator release can be precisely synchronized with rapid cognitive acts[2,11]. Moreover, neuromodulators alter information processing in cortical networks, for instance, by boosting neural gain[1–3]. Thus, even subtle changes in arousal in the awake state can produce selective and diverse effects on cognition[6,12]. For example, in the task used by Eldar *et al.*[6], the degree of arousal did not determine the overall performance level. Rather, arousal determined the extent to which learning was selectively biased toward individual predispositions, as reflected in the structure of neural interactions.

The study by Eldar *et al.*[6] is a showcase for how to link indices of brain-wide neuromodulator release to large-scale neural interactions and cognition. This integrative approach might also uncover the mechanisms by which arousal shapes other cognitive processes, such as decision-making. Furthermore, the approach may provide a glimpse at how cognition is affected when the neuromodulatory systems go awry. For example, a permanent alteration of functional brain networks[13] through the modulatory mechanisms probed by Eldar *et al.*[6] might explain how stress, a state of chronically increased arousal, shifts instrumental behavior from goal-directed to habitual control[14]. In sum, studies like the one by Eldar *et al.*[6] will yield important insights into how neuromodulators orchestrate large-scale neural interactions and cognitive operations in the healthy and diseased brain[5].

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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