Optimizing brain processing

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Cholinergic neurons in the basal forebrain enable alert and attending brain states. A study now shows how basal forebrain activity increases coding abilities of cortical neurons and at what stages these changes occur.

Have you ever wondered what makes the difference between the dreamy drowsy state before nodding off in your easy chair and that crisp appearance of the world when fully alert? A small structure in the basal forebrain, the nucleus basalis, is the key. In conjunction with other subcortical neuromodulatory systems, it has long been thought to promote neocortical 'energizing', allowing the cortex to rapidly handle changing task demands and inputs. Artificial activation of the nucleus basalis results in desynchronization of neocortical activity[1], resembling states seen in alert and attending subjects[2]. Nucleus basalis neurons alter their activity in a task- and stimulus-dependent manner, release of acetylcholine (its main transmitter) in the cortex is tightly linked to states of attention[3], and blockade of specific cholinergic receptors reduces attentional modulation of cortical activity[4]. But how does nucleus basalis activation and associated acetylcholine release alter brain states? How do they affect cortical processing and in what sense do they optimize brain processing? Many, often contradicting, answers have been given to these questions over the years. An exciting addition to the story is given by Goard and Dan in this issue[5]. They found that nucleus basalis activation increased neuronal reliability and decreased the redundancy of information processing. Both changes boosted the amount of information neuronal populations could process at any given time. Decreased redundancy of cortical neuronal activity was mediated through action at muscarinic receptors in the cortex itself, whereas increased reliability was mediated through distributed mechanisms along the subcortical processing pathway. These data suggest potential mechanisms by which the nucleus basalis might 'sharpen' our perception of the world when we are fully alert.

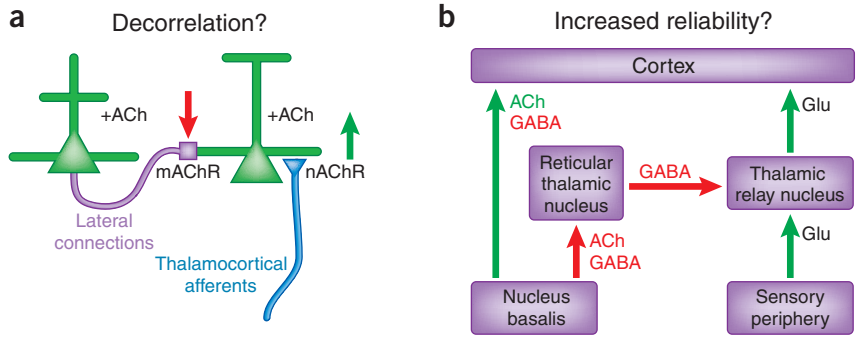

Figure 1 Mechanism by which decreased correlation and increased response reliability could be mediated by activation of the nucleus basalis. (**a**) Cortical neurons make extensive connections in an area (lateral connection) in addition to receiving feedforward input (termed thalamocortical afferents here). These connections can be independently modulated by acetylcholine (ACh). ACh can act on muscarinic receptors (mAChRs) in the presynaptic terminal to reduce their efficacy. This would reduce crosstalk between cortical neurons and consequently affect their correlation, as demonstrated by Goard and Dan[5]. ACh can also increase the synaptic efficacy of thalamocortical synapses by acting on nicotinic receptors (nAChR). This could, in principle, increase response reliability, but Goard and Dan's study suggests an alternative mechanism. (**b**) In addition to its cortical projection, the nucleus basalis has strong connections to the reticular thalamic nucleus, the gatekeeper of the thalamus. The reticular thalamic nucleus inhibits the flow from the sensory periphery to the cortex at the thalamic relay stage. The nucleus basalis can inhibit the activity in the reticular thalamic nucleus through GABAergic and cholinergic mechanisms and could thus control the gatekeeper. An active nucleus basalis would promote the flow from the sensory periphery to the cortex by disinhibiting neurons in the relay nucleus. This could result in increased response reliability in the cortex and the relay nucleus itself, consistent with the results by Goard and Dan[5]. Although the appeal of these schematics lies in their simplicity, many more mechanisms will be at work. Up and down arrows in **a** relate to increased and decreased synaptic efficacy when ACh levels are increased. Green arrows in **b** indicate excitatory connection and red arrows indicate inhibitory connections. The main transmitters involved in the respective transmissions and their predominant respective actions are indicated (green, excitation; red, inhibition). Glu, glutamate.

Goard and Dan[5] tested the role of the nucleus basalis with a crucial, but fairly simple, experiment. They recorded neuronal activity in primary visual cortex simultaneously from multiple neurons and cortical layers while anesthetized rats viewed short movie sequences, and then they asked what changes occurred following stimulation of the nucleus basalis. Electrical stimulation results in increased acetylcholine (and GABA) release at axon terminals and this markedly influenced the responses of visual cortical neurons. First, nucleus basalis stimulation altered the power spectrum of the local field potential in V1, increasing the spectral power at higher frequencies (10–100 Hz) at the expense of lower frequencies, reminiscent of the electroencephalography changes seen in earlier studies[1] and when subjects go from rest state to active states[2]. Nucleus basalis stimulation increased the neuronal activity in layers 4–6, while slightly reducing the activity in layers 2 and 3. Irrespective of increased or decreased activity, neurons responded much more reliably and time locked to specific events in the movie sequences. Intriguingly, the activity of simultaneously recorded neurons was less correlated. Increased reliability increased the amount of information a given neuron could encode, whereas decreased interneuronal correlation reduced the redundancy of information in a pool of neurons. Both mechanisms increased the coding capacity of neuronal populations. The nucleus basalis can thus improve information processing in the cortex.

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What are the mechanisms behind this increased coding ability? Cortical neurons make extensive connections with their neighbors, and the extensive crosstalk is a possible source for correlated activity levels. Acetylcholine can reduce the efficacy of these connections by activating presynaptic muscarinic receptors[6]. Reduced synaptic efficacy of lateral connections would reduce crosstalk and thus decorrelate cortical activity (**Fig. 1a**). To test this scenario, Goard and Dan[5] applied the muscarinic antagonist atropine sulfate. Nucleus basalis stimulation in the presence of muscarinic receptor blockade indeed resulted in less decorrelation of cortical neurons.

The increased response reliability was not affected by muscarinic receptor blockade, but this was hardly surprising. To determine the mechanisms of increased response reliability, one might rather want to direct attention to nicotinic receptors in visual cortex, which reside mostly on thalamocortical terminals. The activation of these receptors increases thalamocortical transmission efficacy[7]. Thus, incoming stimuli should be processed more effectively when nicotinic receptors are activated by acetylcholine. However, when Goard and Dan[5] tested this possibility by blocking the nicotinic receptors, they found no reduction in response reliability when nucleus basalis was electrically stimulated. This finding suggests that the increased response reliability associated with nucleus basalis stimulation occurs at subcortical stages before the information reaches the cortex. Goard and Dan[5] confirmed this by recording from the lateral geniculate body of the thalamus with and without nucleus basalis stimulation. Nucleus basalis stimulation resulted in increased response reliability at this stage of processing. These data suggest that the nucleus basalis affects neuronal activity at different levels and has a variety of ways to constrain how information is processed.

One way that the nucleus basalis could alter response reliability at the subcortical level is through its connections with the thalamic reticular nucleus. The thalamic reticular nucleus is often viewed as a gatekeeper that controls the entry of signals to the cortex[8]. An active thalamic reticular nucleus inhibits thalamic relay nuclei and thus the flow of sensory information to specific cortical areas. Notably, the nucleus basalis can inhibit neurons in the thalamic reticular nucleus through its GABAergic and cholinergic projections[9], thereby disinhibiting the thalamic relay nucleus and providing the cortex with sensory input (**Fig. 1b**). Does the nucleus basalis control the gatekeeper?

The effects of acetylcholine on cortical and subcortical activity have been of interest for quite some time. Early studies have suggested that acetylcholine application and nucleus basalis stimulation can increase the signal-to-noise ratio of neuronal responses[10] and sharpen tuning curves[10], effects that, at first glance, are reminiscent of the increased response reliability reported by Goard and Dan[5]. However, the authors were unable to find systematic alterations of tuning characteristics of cortical neurons, which is consistent with some recent reports[11]. Future studies are required to determine the reasons for these discrepant results.

How do these findings relate to states of attention? This simple question opens a can of worms. Although there are notable similarities between the effects seen here and those reported when animals are engaged in attention-demanding tasks, there are also differences or at least open questions. The increase in gamma power in the LFP that was induced by nucleus basalis stimulation is reminiscent of increased gamma power seen in macaque V4 and frontal eye fields[12] when attention is directed to the receptive field of the neurons being studied. But is this increase with attention supported or mediated by cholinergic mechanisms? The increased response reliability is compatible with the effects of attention, where attention increases the firing rate and can reduce the response variance[13]. However, the finding that nucleus basalis stimulation reduces activity in layer 2/3 of V1 is incompatible with results from V1 in task-performing monkeys[4]. As to decorrelation of activity, recordings from V1 show that correlation between neurons is not decreased with attention[14], suggesting that different mechanisms are at work. However, it was recently found that correlation of activity between V4 neurons was reduced when attention was directed to their receptive field[15]. The closest direct link between attention and this result is the finding that attentional modulation in V1 of the macaque requires active muscarinic receptors. In one study[4], blockade reduced attentional modulation in V1. But this study[4] did not analyze whether muscarinic blockade reduced decorrelation or whether acetylcholine application caused a decorrelation. In addition, response reliability did not seem affected in this study[4], so the validity of this link remains to be determined.

The list of open questions clearly does not end here, but this short list demonstrates how much more there is to be learnt before we arrive at a mechanistic account of how the nucleus basalis, acetylcholine and attention modulate visual cortical processing. The study by Goard and Dan[5] contributes some important information to this area of study and maybe even suggests how the nucleus basalis helps to abolish that afternoon drowsiness.

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