descending neural controls) can rapidly and perhaps uniformly influence the information-processing state throughout the cerebral cortex. This is in keeping with the behavioral affiliations (for example, vigilance, motivation, mood, and memory) that have been attributed to these nuclei (*3*). It appears that the principle of asymmetrical neural feedback may be an important common denominator in the neuroanatomical organization of behavioral states.

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Response: Mesulam (*1*) emphasizes interesting and important similarities between the anatomic circuitries of the noradrenergic nucleus locus coeruleus (LC) and the cholinergic nucleus basalis systems. Both groups of cells widely innervate the neocortical mantle and thereby presumably exert global influences on cortical processing. However, there is a marked asymmetry in the neocortical connections of these cell groups: the LC receives no direct input from neocortical areas, and the basalis receives direct input from only a few.

Mesulam proposes that such asymmetrical circuitry may also hold for other nonthalamic cortical afferents and that a principle of asymmetrical neural feedback may characterize anatomic circuits involved in the organization of behavioral states. While this is an intriguing suggestion with substantial merit and is similar to our own functional analyses (*2, 3*), there are additional considerations. For example, brain areas other than the nonthalamic cortical afferent nuclei are asymmetrically connected with their targets, but may lack direct involvement in behavioral state processes (for example, retinal-thalamic and cortico-tectal pathways). The same is true for some cortical afferents, such as the occipital cortex, which projects to frontal, temporal, and parietal lobes but itself receives few reciprocal projections. Thus, other factors, such as functional attributes of afferents to, and discharge properties of, the neurons in question, must also be considered in functional analyses.

In this context, we have found that there are pronounced physiological differences between LC and basalis neurons in both rats and monkeys. LC cells are markedly homogeneous for physiological properties, exhibiting slow impulse conduction velocities, characteristic wide spike waveforms, tonic changes in activity as a function of behavioral state, and phasic responses to a wide array of sensory stimuli (*3, 4*). The major afferents to LC receive inputs consonant with these properties; for example, paragigantocellularis receives inputs from many sensory modalities (*5*) and it potently excites LC cells (*6*), indicating that this nucleus may serve as the sensory relay area for LC phasic activity (*2, 3*). In contrast, cortically projecting nucleus basalis neurons are markedly heterogeneous in terms of impulse conduction velocity, spike waveforms, spontaneous activity, and certain sensory-behavioral discharge properties (*7, 8*). Taken together, these results suggest that individual LC neurons are homogeneous in terms of intrinsic physiologic properties and afferent control, resulting in concerted discharge properties, while nucleus basalis neurons may be heterogeneous along these same dimensions. There are also differences in the patterns of cortical termination by these two cell groups: individual LC neurons broadly innervate different cortical areas (*4*), while single basalis neurons have more restricted cortical terminal fields (*7, 9*).

These anatomic and physiological distinctions may indicate significant functional differences between the LC and basalis systems. Thus, LC neurons may act more or less in unison to exert a concerted, global influence on brain activity and behavioral state [for example, vigilance (*3, 10*)], while basalis neurons, by virtue of their physiological heterogeneity and restricted terminal fields, may exert more differentiated control of select target areas (*7*). Additional studies of these two important cortical afferents are needed to further delineate their properties and to help determine whether functional similarities outweigh the differences.

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