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The Functional Neuroanatomy of Awareness: With a Focus on the Role of Various Anatomical Systems in the Control of Intermodal Attention

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This review considers a number of recent theories on the neural basis of consciousness, with particular attention to the theories of Bogen, Crick, Llinás, Newman, and Changeux. These theories allot different roles to various key brain areas, in particular the reticular and intralaminar nuclei of the thalamus and the cortex. Crick's hypothesis is that awareness is a function of reverberating corticothalamic loops and that the spotlight of *intramodal* attention is controlled by the reticular nucleus of the thalamus. He also proposed different mechanisms for attention and intention (''will''). The current review presents a new hypothesis, based on elements from these hypotheses, including *intermodal* attention and olfaction and pain, which may pose problems for Crick's original theory. This work reviews the possible role in awareness and intermodal attention and intention of the cholinergic system in the basal forebrain and the tegmentum; the reticular, the intralaminar, and the dorsomedial thalamic nuclei; the raphe and locus coeruleus; the reticular formation; the ventral striatum and extended amygdala; insula cortex, and other selected cortical areas. Both clinical and basic research data are covered. The conclusion is reached that the brain may work by largely nonlinear parallel processing and much intramodal shifts of attention may be effected by intracortical, or multiple corticothalamic mechanisms (small local ''flashlights'' rather than one major ''searchlight''). But this is constrained by the functional anatomy of the circuits concerned and waking ''awareness'' is modulated by the many ''nonspecific'' systems (cholinergic from the basal forebrain, noradrenergic from the locus coeruleus, dopaminergic from the substantia nigra and ventral tegmentum, and serotoninergic from the raphe). But the principal agents for intermodal attention shifts, the ''searchlight,'' may be two key nuclei of the cholinergic system in the mesencephalon. Clinical loss of consciousness results from damage to these nuclei but not from damage to the cholinergic nucleus basalis of the basal forebrain.

INTRODUCTION

Various theories about the neural basis of consciousness (awareness) have recently been put forward. One school (e.g., Crick, Bogen) hopes to discover ''consciousness neurons'' whose activity is necessary and sufficient for particular conscious experiences to occur. Another school (e.g., Kinsbourne, Dennett) denies that any such neurons exist. Their theory states that consciousness is an emergent property of a large, interconnected network of competing, parallel processors and that consciousness is located wherever the action is (what Kinsbourne calls a ''dominant locus''). How-

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ever, as Baars (1995) indicates, all neurons may be equal but some neurons are more equal than others. He says there are only two loci in the brain where a small lesion can result in loss of consciousness: the mesencephalic RF[2] (MRF) (Moruzzi & Magoun, 1949) and the intralaminar thalamic nuclei (ILN) (Bogen, 1995a, 1995b). Many discussions of the mechanisms of conscious awareness, moreover, quickly turn into discussions about the mechanisms of selective attention. Furthermore it is essential to distinguish between brain structures that are essential for consciousness *as such* (such as the RF) and those that *modulate* the content of consciousness.

Francis Crick (1984, 1994) has suggested that the neurological basis of consciousness or ''awareness'' lies in reverberating activity in cortico-thalamic loops (for his definition of ''awareness,'' see Crick, 1994). This hypothesis was adumbrated by Campion and Elliot Smith (1934) and by Cobb (1943). Crick also suggested that the reticular nucleus of the thalamus (nRt) controls the ''searchlight'' of attention. He noted that this nucleus sits astride all thalamo-cortical connections and so could monitor this traffic and direct attention by its inhibitory GABAergic input to all other thalamic nuclei. He also distinguishes between sensory ''awareness'' or *at*tention and motor *in*tention (or ''will'') as separate components of consciousness and based on different circuits in the brain. (Some psychologists have disputed this division and regard ''attention'' as a unitary motor function. However, we can shift our attention without any overt movement and the unitary theory fails to give an adequate account of the difference between clinical disturbances of voluntary shifts of sensory attention and akinetic mutism.) Llinás and Paré (1991) add a detail in that they suggest that the *content* of consciousness may lie in loops involving the specific thalamic relay nuclei, and the ''binding'' of these into a ''unitary experience'' involves the intralaminar thalamic nuclei (ILN). Other theories have been put forward by Changeux (1985) and Zeki (1992). The former suggested that nerve nets based on the chemospecific nuclei in the brain stem (PPT, LDT, LC, raphe, and the dopaminergic A10 nucleus in the tegmentum) form a ''surveillance system'' that functions ''as a whole,'' linked by oscillatory activity. ''Consciousness *is* the functioning of this regulatory system.'' Zeki has located visual awareness in V1 itself. However, recent evidence from Zeki's group (Barbur, Watson, Frackowiak, Zeki, 1993) indicates that V1 is not necessary for visual awareness, at least of moving stimuli.

A more detailed ''gating theory'' has been put forward by Newman (1995). In this, the lowest level gate is provided by the reticular formation (RF), whose multimodal neurons form ''saliency maps'' of the meaningful environment. The RF projects strongly to the nRt and modulates rhythmic high-frequency patterns of activation and so facilitates (or blocks) the flow of relevant sensory information through the many gatelets of the nRt. These gatelets form a second-level gate that switches appropriate cortical areas on and off when needed. These gatelets also have a con-

[2] Abbreviations used: ILN, intralaminar nuclei of the thalamus; LC, locus coereleus; LDT, lateral dorsal tegmental nucleus; LGN, lateral geniculate nucleus; MD, dorsomedial nucleus of the thalamus; MRF, mesencephalic reticular formation; NB, nucleus basalis of Meynert; nRt, nucleus reticularis of the thalamus; PCPA, parachlorphenylalanine; PPT, pedunculopontine nucleus; RF, reticular formation; S II, secondary somatosensory cortex; V I, primary visual cortex; V Mpo, n. ventralis medialis (posterior) of the thalamus.

verging input from the prefrontal cortex, posterior sensory cortex, and superior colliculus. They represent the controls on Crick's searchlight of attention. Newman allots the role of thalamic ''relay nuclei'' to the ILN (relays from the MRF to the cortex), as well as mediating the conscious experience of pain and initiating visually guided movements. The ILN for Boden play a key role in directing sensory attention; for Kinsbourne they coordinate attention and action; for Crick, as we saw, they mediate *in*tention. Other systems are, of course, involved in attention, for example, for vision, the pulvinar, parietal cortex, and superior colliculus (Posner, 1994), but in the theories we have been looking at, the nRt plays a key role.

However, a problem arises when one considers olfaction. Whereas audition, somatic sensation, and taste have a similar neuroanatomical basis to vision, and presumably a similar neuroanatomical mechanism mediating selective attention, olfaction has a very different one. Moreover, Crick's hypothesis does not consider directly how we switch attention (''awareness'') between vision and the other sensory modalities, nor does it deal with qualia. The purpose of this review is to examine these topics.

The Functional Neuroanatomy of Olfaction and Pain and Its Implications

The olfactory bulb, which many consider to be the olfactory equivalent of the retina, projects to the primary olfactory areas, which include the pyriform allocortex and the cortical nucleus of the amygdala, without an intermediate thalamic relay. From here projections lead to the central portion of the dorsomedial nucleus of the thalamus (MD), the subthalamic nucleus, and the postero-lateral hypothalamus. There are also direct connections from the olfactory bulb to the agranular insular cortex. Most of these regions also project back to the olfactory bulb. There are also direct connections to the olfactory bulb and primary olfactory cortex from the locus coeruleus (LC), the raphe nuclei, and the cholinergic nucleus basalis (NB) of the forebrain and lateral dorsal tegmental nucleus of the midbrain (LDT). Cholinergic basal forebrain inputs to the olfactory bulb inhibit inhibitory interneurons and facilitate the transmission of olfactory bulb output to higher centers (Elaagouby, Ravel, & Gervais, 1991). The olfactory portion of MD projects to the central posterior orbitofrontal cortex, whereas the olfactory portion of the hypothalamus projects to the lateral posterior orbitofrontal cortex. These cortical areas project in turn to other polysensory areas of the frontal lobe. The primary olfactory cortex also projects robustly directly to these orbitofrontal areas in an orderly laminar array. There is also an important projection from the olfactory bulb to the lateral habenular nucleus.

Experimental evidence indicates the following functional properties of these anatomical structures in olfaction: lesions (but only very extensive ones—presumably because of their high degree of plasticity) of the olfactory bulb lead to anosmia. Stereotactic lesions of MD in the rat do not lead to anosmia but only to the inability to acquire complex olfactory discrimination tasks (Slotnick & Schoonover, 1992). In the earliest study in this field Allen (1940) ablated in dogs the frontal lobe, hippocampi, and the occipito-parieto-temporal cortex, sparing only the pyriform areas. He found that the animals could no longer discriminate powerful odorants such as cloves from asafetida, but they could still locate meat by smell. He suggested that the pyri-

form cortex by itself could still detect biologically important odors. Price and Slotnick (1983) suggest that MD together with its orbitofrontal projection area may not be involved with olfactory processing but in mediating a variety of higher-level functions involving olfactory-guided behavior. Zatorre and Jones-Gotman (1991) report the effect in 106 patients with epilepsy of temporal and frontal lobectomies. All patients showed normal detection thresholds for *n*-butyl alcohol and thus apparently no loss of ''awareness.'' But they developed loss of discrimination between different stimuli. Temporal lobectomy (which included the uncus and amygdala) produced an ipsilateral defect whereas frontal lobectomy (especially R) produced a bilateral deficit (see also Carroll, Richardson, & Thompson, 1993; Bellas, Novelly, & Eskenaz, 1989).

Price, Slotnick, and Revial, (1991) suggest that the dorsomedial thalamic nucleus (MD) (and associated cortex) is implicated in olfactory discrimination and complex learning whereas the hypothalamus mediates the autonomic and neuroendocrine aspects of olfactory-guided behaviors (e.g., feeding, aggression, reproduction). Furthermore, Russchen, Amaral, and Price (1987) drew attention to the fact that the major projection from the pyriform cortex to the olfactory part of the orbitofrontal cortex is direct and not via the dorsomedial thalamic nucleus. This led them to propose that a corticocortical pathway rather than a transthalamic pathway might serve to relay detailed sensory information to the neocortex. Otto and Eichenbaum (1992) found that lesions of the orbitofrontal cortex impair the acquisition of olfactory-related behaviors, whereas lesions of the entorhinal cortex had no effect on acquisition but impaired performance. The site of long-term olfactory memory storage, in the rat at least, seems to be in the pyriform cortex and olfactory bulb (Mouly, Kindermann, Gervais, & Holley, 1993). The olfactory habenular pathway is involved in integrating olfactory information with food-getting behavior (Rausch & Long, 1971). Lesions of the habenula have no effect on the acquisition of olfactory-related behaviors but impair olfactory-related performance (Mok & Mogenson, 1974). Lesions of the diagonal band cause disturbances in olfactory, memory-based behavior but have no effect on odor detection (Paolini & McKenzie, 1993).

On the basis of this evidence, Barr and Kiernan (1993) conclude that the primary site for ''awareness of olfactory stimuli'' lies in the pyriform cortex. Koger and Mair (1994) conclude that experimental studies have shown that lesions of olfactory thalamocortical pathways spare primary sensory capacity and affect only the rate at which some odor-guided behaviors are learned. If this hypothesis is correct then awareness of olfactory stimuli cannot be a function of reverberating thalamo-cortical circuits, since, at this level, there are none. It could depend on reverberating circuits between the olfactory cortex and the olfactory bulb. But the reticular nucleus of the thalamus (nRt) does not have any projection to the olfactory bulb or the pyriform cortex. The dorsomedial nucleus of the thalamus (with which nRt does have contact) may get involved only with complex olfactory discriminations, not basic awareness. Yet, to introspection, we seem to be able to switch attention to an olfactory stimulus as easily as we can to any other. Of course the mechanism mediating the switch of attention within one modality may be different from that needed to switch attention in another

modality, between two different modalities, or between different behaviors (Milner & Goodale, 1993).

However, the odorant used in almost all of these threshold studies was *n*-butyl alcohol. This, as Zatorre and Jones-Gotman (1991) themselves state, ''probably'' also stimulates the trigeminal nerve endings in the nasal mucosa, which might complicate any conclusions about olfactory thresholds (Laing, 1985). However, the threshold of the trigeminal nerve for *n*-butyl alcohol is high and this factor is probably unimportant (R. G. Mair, personal communication). But one study (Rausch & Serafetinides, 1975) that used other odorants (pyridine, phenethyl alcohol, and pentylacetate) in temporal lobectomy patients, found that they had abnormally *high* detection thresholds. Controls could detect odors too weak to be identified ($p < .01$) but the patients could detect an odor only strong enough to be identified. The portions of the anterior temporal lobe removed included the uncus, amygdala, and portions of the hippocampus, hippocampal gyrus, and fusiform cortex. Of these only the amygdala (cortical nucleus) and overlying uncus have known olfactory functions, and the pathway from the olfactory bulb to the amygdala does not run through the thalamus either. Clearly, more work needs to be done. Furthermore, olfactory ''awareness'' could be distributed across both the orbitofrontal cortex and the uncal region so that removing either would not affect olfactory ''awareness.'' However, one paper (Jones-Gottman & Zatorre, 1988) reports that patients with lesions of both the orbitofrontal cortex and the temporal pole performed no worse in olfactory tests than those with lesions of only the former. So, it is clear that the bulk of these data, as they stand, suggest that Crick's theory, or any theory claiming an essential role for nRt in selective attention, cannot apply to olfactory awareness.

Moreover, ''awareness'' may be organized on a hierarchical rather than an all-or-none basis. Head and Holmes (1911), to explain thalamic pain, suggested that basic awareness of pain is literally located in the medial thalamus—a suggestion supported by Bartlet (1951). In many cases this type of severe causalgic (or ''protopathic'') pain in response to a pinprick is distributed diffusely over the entire hemibody and results from cutting some of the connections between the cortex and thalamus, either by a lateral thalamic lesion (nucleus ventralis posterior) (Boivie, 1994), or by a lesion in the white matter deep to the insula and opercular region of the posterior parietal cortex (Schmahmann & Leifer, 1992). On Crick's theory one might expect the result of cutting the pain pathway between the thalamus and the cortex to be anesthesia not thalamic pain. However, there are multiple pain pathways, particularly between the medial thalamus and the cingulate and insular cortices that probably mediate (via reverbatory circuits) the conscious experience of pain more than the lateral pathway does.

There is further evidence to suggest that the insula seems to be involved as an essential player in the conscious awareness of pain (Schmahmann & Leifer, 1992). Berthier, Starkstein, and Leiguarda (1988) describe six cases of cerebral damage with ''asymbolia'' for pain. In all cases the insula was damaged and in two the secondary somatosensory cortex was spared. One case showed a small lesion confined to the insula and the neighboring parietal cortex (the operculum). These patients showed no primary sensory deficits and had normal pain detection thresholds. They could

recognize painful stimuli and could distinguish between sharp and blunt stimuli. But the ''qualia'' for pain had vanished. They showed no withdrawal response and had absent or inadequate emotional responses not only to painful stimuli but also to threatening gestures (e.g., no blink or flinch response to a fist approaching the eye) and in five out of six cases no normal response to verbal menaces. They were quite unconcerned about the deficit and seemed unable to learn defensive or escape reactions. Some even laughed during the ''painful'' stimuli and had a tendency to injure themselves as they did not respond appropriately to, for example, putting a hand on a hot stove. However, they showed normal autonomic responses to painful stimuli.

The insula connects the sensory cortex (somatic, auditory, visual) with the basolateral and basomedial nuclei of the amygdala in both directions. It also receives a major input from the medial thalamus and from the pain-specific nucleus (posterior part of the ventromedial nucleus) in the lateral thalamus (Craig, Bushnell, Zhang, & Blomqvist, 1994; Craig, Krout, & Zhang, 1995). The insula is thus clearly essential for the conscious experience of actual pain. Patients with insula lesions can still detect some of the epicritic properties (detection threshold, location) of the stimulus that would normally lead to the feeling of pain but they fail to feel any actual pain. Nor do they appreciate the significance of threats. Lesions of the amygdala, thalamus, or of the cortex do not result in pain asymbolia. So the function of the insula in producing the actual pain would not appear to depend on circuits connecting the insula with these structures.

In somatic sensation, Head and Holmes (1911) also described a ''thalamic'' component of awareness. Patients with damage to the cortex (always including the sensorimotor cortex), no matter how extensive, if touched, could report that something had happened to them, but could not say what or where.

Cairns (1952), on clinical data, in particular a study of anencephalic humans, suggested that crude awareness is based on the diencephalon; such people have ''at best a vague rudimentary awareness, chiefly through the special senses and viscera, with a limited range and crude quality of analysis,''—what Daly and Love (1958) call ''the dim and flickering perceptions'' of decorticate humans. Jason Brown's (1988, 1991) theory of microgenesis and Edelman's (1989) theory of ''primary consciousness'' suggest much the same. Penfield's well-known concept that the brain-stem reticular activating system forms the ''highest level'' of function in the nervous system was cogently criticized by Walshe (1957). But we are dealing here not so much with ''higher'' functions as with the brain mechanisms that construct ''awareness,'' direct attention, and coordinate the manifold activities of the rest of the brain so that consciousness avoids James's ''booming, buzzing confusion'' and so that the organism can proceed with a single, orderly, goal-directed program and pattern of thought and action.

Dennett (1991) has pictured the brain as operating with an array of semi-independent parallel processors that compete at the motor end of things to direct behavior, but do not interact much to form one common organizational structure. As he says, there is no place in the brain, no ''Cartesian theatre,'' where it all gets together. That may be partly true, but one should also look for some central ''switching'' mechanism(s) that supervise, in an orderly way, the recruitment of different brain mechanisms to deal with an ever changing stream of differing environmental chal-

lenges at different levels of complexity and in several different sensory channels. The function of the reticular formation can be likened to that of the supervisor of a computer, integrating its manifold and complex parts as efficiently as possible to deal with a variety of programmes.

Of course, if the brain operates entirely by nonlinear (chaotic) dynamics then there may not be any need to invoke any such central control mechanism. In nonlinear dynamic systems the order reached derives from direct interactions among elementary units. Globus (1992) has reviewed such noncomputational cognitive systems based on nonlinear dynamics. John (1979) and Freeman (1994) have developed similar theories. As John (p. 16) says, ''It is not the location of cells that matters, but rather the rhythm at which they fire. . . . Cells combine to perform mental functions by a statistical process. . . . Every mental operation, including consciousness itself, is due to activity throughout the brain.'' The key, he suggests, is the signal-to-noise ratio. The stroboscopic patterns may represent direct access to such nonlinear processes in the visual brain (Smythies, 1959/1960; Stwertka, 1993). However, it has not been established that the brain operates *entirely* by nonlinear dynamics. Even if it did, anatomy is still important.

If we look first at attention within a single sensory system the picture has already become very complicated. The visual system has been most studied and theories abound in this field. The Posner (1994) model of intramodal visual attention mechanisms (and their variants) are based on the superior colliculus, the pulvinar, and the parietal cortex rather than on nRt. Auditory and somatic sensation may have similar complex systems involving thalamo-cortical and subcortical circuits and synchronized 40-Hz rhythms. These systems share with vision the need to localize the stimulus in external or internal space. There is, however, no such thing as the intrinsic localization of an olfactory sensation. That is to say that visual, somatic, and auditory sensations have intrinsic phenomenal locations in their respective fields, but an olfactory sensation does not. We can discover the origin of an olfactory stimulus, but the primitive olfactory sensation in itself lacks location in a field. So perhaps that is why olfaction does not need any complex ''epicritic'' thalamo-cortical circuits.

We tend, normally, to attend to what is significant in the sensory input. So how is the input tagged with significance? Furthermore we can ask what could be the neuroanatomical system(s) responsible for the intermodal direction of attention as well as for basic ''awareness'' itself?

Obvious candidates are the ascending reticular activating system, the cholinergic tegmental nuclei, the cholinergic nucleus basalis of Meynert in the basal forebrain, with contributions from the raphe nuclei and locus coeruleus (all of which project extensively to the pyriform cortex), and the glutamatergic intralaminar thalamic nuclei. I will consider first what is currently known about the functions of these with respect to the problem in hand.

The Cholinergic System

The cholinergic nuclei of the basal forebrain are the nucleus basalis of Meynert (NB), the vertical and diagonal limbs of the diagonal band of Broca (that connect the septal nuclei and the amygdala), and the medial septum. (The former is the domi-

nant locus in primates as compared with rat [Gaykema, Van Weeghel, Hersh, & Luiten, et al, 1991].)

The NB provides the sole cholinergic input to the cortex, projecting to all areas (Bickford, Günlük, Van Horn, & Sherman, 1994). It also projects to nRt by GABAergic (Asanuma & Porter, 1990; Bickford et al., 1994) and some cholinergic neurons (Steriade, Parent, Paré, & Smith, 1987), and to the amygdala by GABAergic neurons.

The major afferents to NB come from the pontine pedunculopontine nucleus (PPT) and the lateral dorsal tegmental nucleus (LDT), from the cortex in an ordered topographic array, particularly from limbic cortex (Záborszky, Cullinan, & Braun, 1991), and from the ILN, substantia nigra, raphe, and locus coeruleus (Woolf, 1991). There is also a GABAergic input from the intercalated cell masses of the amygdala (Paré & Smith, 1994). The ILN, medial part of MD, and nRt receive additional cholinergic input from NB (Steriade, Domich, & Oakson, 1986; Steriade, Jones, & Llinás, 1990). There are extensive bidirectional connections between NB (and other cholinergic nuclei of the basal forebrain) with the prefrontal cortex.

The cholinergic nuclei in the peribrachial region of the tegmentum of the midbrain (and adjacent pons) are the pedunculopontine tegmental nucleus (PPT) and the lateral dorsal nucleus of the tegmentum (LDT). The main input to the PPT and LTD includes the (limbic) nucleus accumbens, hypothalamus, ILN, raphe, and particularly the pontine and medullary RF (probably by a glu/asp system). Their main output includes NB, all thalamic nuclei, amygdala, and the primary olfactory cortex (Steckler, Inglis, Winn, & Sahgal, 1994). All thalamic nuclei get cholinergic input from PPT and LDT (Jones, 1988). Axons from the peribrachial tegmental region (PPT and LDT) form particularly complex triangular synapses in the LGN in which retinal and interneuron terminals and X relay cell axons are linked closely to the tegmental input, suggesting that the latter maintain a prominent gating function on the relay of information to the cortex (Sherman, 1988).

Owing to the fact that neurons in NB are severely degenerated in Alzheimer's disease, it has widely been assumed that the cholinergic innervation of the cortex has mainly to do with memory. However, other functions for this system have been suggested. These include the enhancement of sensory-evoked activity (Baskerville, Chang, & Herron, 1993), attention processes (Inglis, Day, & Fibiger, 1994a; Inglis, Dunbar, & Winn, 1994b; Muir, Dunnett, Robbins, & Everitt, 1992; Muir, Page, Sirianathsinghi, Robbins, & Everitt, 1993) and responding to the significance and reinforcement value of stimuli (Paré & Smith, 1994). Behavioral arousal is associated with increased tonic firing of NB neurons, ACh release in the cortex and desynchronization of the EEG. Stimulation of NB leads to an increase of field potentials, single neuron discharge rates, and EPSPs in the cortex all of which lead to cortical arousal (Metherate & Ashe, 1993). All these effects are blocked by intracortical atropine. ACh enhances neuronal responsiveness and directional sensitivity in the cortex, especially when paired with somatic or visual stimuli, without affecting background activity. It may also excite inhibitory interneurons and so increase directional specificity in that way (Bassant, Baleyte, & Lamour, 1990; Murphy & Sillito, 1991). Rats with decreased cortical ACh are impaired in tasks testing for sensory processing not memory (Juliano, Ma, Bear, & Eslin, 1990). In slow wave sleep NB neurons cease firing. During waking they discharge tonically at 20 Hz for long periods. NB neurons re-

spond to behaviorally significant stimuli and a significant proportion encode the reinforcement value of stimuli (Paré & Smith, 1994). Chemoinactivation of NB by locally applied muscimol induces an attention deficit in perceptual processes but no change in the selection of response strategies (Pang, Williams, Egeth, & Olton, 1993). Cholinergic input to the entorhinal cortex from the horizontal limb of the diagonal band may act as an attention modulator that labels which incoming information is important (Johnson & Kesner, 1994).

Patients with Alzheimer's disease have attention deficits as well as dementia. Patients with olivopontocerebellar disease and Parkinson's disease show a marked decrease for markers for the basal forebrain cholinergic system but no dementia. Alzheimer patients have abnormalities in other cortical and subcortical systems besides NB.

Cholinergic systems may be related to memory in other areas, for example, the cholinergic septal-hippocampal projection for spatial short-term memory. The cholinergic projection from the diagonal band of Broca to the cingulate cortex mediates the later stages of visual discrimination learning (Muir et al., 1993). The memory disturbances produced by excitotoxic lesions of cholinergic basal forebrain nuclei correlates with loss of acetyltransferase activity in the amygdala rather than the cortex (Boegman, Cockhill, Jhamandas, & Beninger, 1992); so the projection from this region to the cortex may subserve attention and to the amygdala may subserve memory.

The relation between NB and motivation is illustrated by the fact that the superior parietal lobule contains a group of cells that have no apparent sensory input but that discharge strongly whenever the monkey makes a movement aimed at reaching for an object it wants. These cells do not fire in response to the same movement made without the motivation. It is thought that these cells are responding to input from NB and cingulate cortex (Steriade et al., 1990).

Steriade (1992) points out that a large area anterior to PPT and LGN in the rostral midbrain core, where the neurotransmitters concerned are as yet unknown (but are possibly glu/asp), also contributes to activation of thalamic neurons. No attempt is made in this review to cover the large number of polypeptides involved in all these mechanisms. This would require a review of its own.

Steininger, Rye, and Wainer (1992) allot a fundamental role to the cholinergic pedunculopontine nucleus of the tegmentum (PPT) in functional neuroanatomy. It may modulate motor systems in relation to the behavioral state of the animal by its projection to the substantia nigra. It may also modulate sleep function. Its ascending efferents to the thalamus may modulate thalamo-cortical transmission and cortical desynchronization. Its projections to the hypothalamus and basal forebrain (NB) may also promote cortical desynchronization by their diffuse cortical projections. Its descending connections to the pontine RF are related to the pontine-geniculate-occipital waves, rapid eye movements, and muscle atonia of REM sleep. This projection goes directly to the gigantocellular tegmental field in the medial pons. Carbachol injections into this nucleus produce typical REM sleep. This projects in turn to the pontine parabrachial nuclear complex (Kollicker-Fuse nucleus and a medial and lateral parabrachial division on either side of the brachium conjunctivum) which contains the ''REM-on'' and ''REM-off'' cells (Gilbert & Lydic, 1994).

Since lesions of NB do not lead to loss of consciousness whereas lesions of PPT and LDT do, the latter would seem to be essential ''consciousness'' neurons and

the former ''consciousness modulatory'' neurons. So PPT and LTD provide a good candidate for our role. They connect with all cortical areas (via NB, which forms the sole cholinergic input to the cortex and possibly some directly via noncholinergic mechanisms), to key thalamic nuclei (including ILN, and to nRt by both cholinergic and GABAergic projections), and their activities are associated with cortical arousal in both REM and waking. Presumably the basal forebrain and the tegmental divisions of the cholinergic system play different but related roles in ''awareness.'' Possibly the latter mediates a global ''on–off'' function. Lesions in the midbrain and pontine RF reliably lead to loss of consciousness in a way that lesions elsewhere do not. The basal forebrain may take care of the fine-tuning of awareness with respect to the significance and meaning of stimuli.

Pharmacological data support a key role for the cholinergic (muscarinic) system in awareness. Drugs that act on the dopamine and norepinephrine systems produce mainly changes in alertness (amphetamine), reinforcement (cocaine), and mood (some antidepressants). Drugs that act on the serotonin system produce widespread changes in perception (LSD) or mood (other antidepressants). Nicotine is a cholinergic drug of addiction acting on alerting and reinforcement mechanisms. Drugs that act on the muscarinic cholinergic system (atropine, muscarine) produce delirium (Ardila & Moreno, 1991). Combined blockade of central serotonin and acetylcholine systems by PCPA and atropine lead to a profound dementia-like state but not to coma or sleep. Vanderwolf (1987) deduced from this that cortical arousal is primarily a function of 5 HT and ACh systems and that NE plays a secondary role. Coma itself is, however, not a good guide as it is produced by many agents that interfere with global brain function such as general anesthetics, hypoglycemia, and concussion.

Thus the cholinergic system, with its two functionally different subdivisions, remains high on what Crick would call our list of suspects.

The Reticular Nucleus of the Thalamus

Crick's pioneer ''searchlight'' theory of the neuroanatomical basis of attention and awareness allotted a key role to this nucleus, which, in spite of its name, is not a part of the reticular formation. It forms a thin sheet of cells wrapped around the rest of the thalamus astride its input and output channels, as explained above. It consists exclusively of GABAergic neurons that project to all other thalamic nuclei but not at all to the cortex. It has a powerful projection to the ILN but less to specific relay nuclei and MD (Steriade, Parent, & Hada 1984). The nRt receives excitatory axon collaterals from the thalamocortical and corticothalamic axons that pass through it. nRt also has the GABAergic and cholinergic inputs from NB I mentioned earlier as well as GABAergic input from the pallidum and the substantia nigra (Hazrati & Parent, 1991; Paré, Hazrati, Parent, & Steriade, 1990).

In the specific thalamic relay nuclei electron microscope evidence (Montero & Singer, 1985; Ohara, Sefton, & Lieberman, 1980) shows that nRt neurons synapse robustly by inhibitory synapses directly onto the intraglomerular dendrites and cell bodies of thalamic relay neurons as well as onto the dendrites of the inhibitory interneurons. In the thalamic ventroposterior nucleus 82% of nRt cells synapse onto dendrites of relay cells, 8.5% onto dendrites of interneurons, and 7.3% onto somata

(Liu, Warren, & Jones, 1995). There are three types of terminal involved (Takács, Hámori, & Silakov, 1991): $F1_1$ (from nRt), which synapse mainly on relay cells; $F1_2$ (from interneurons), which synapse equally on relay cells and interneurons; and F2 (from and to interneurons), which make dendrodendritic contacts. Spreafico, Frassoni, Arcelli, and De Biasi, (1994) and Bickford et al. (1994) suggest that nRt neurons inhibit the firing of relay cells and so form a negative feedback system. Spreafico et al. suggest that the interneurons may control the ''quality'' rather than the quantity of information forwarded to the cortex. In contrast, La Berge (1990) and Steriade et al. (1986) suggest that the important connection is the one with the interneurons so that the nRt mediates positive feedback.

An alternative suggestion was made by Sherman and Koch (1986, 1990). As Crick (1984) had pointed out, a simple negative feedback loop would mean that the activated relay cell would be shut off, whereas the spotlight theory of attention would seem to require that it be switched on. So Sherman and Koch suggested that the nRt projects not to the active cells in the LGN but to neighboring ones, which it inhibits by F1 synapses, thus promoting the former in the competition to get to the cortex. This fits the electron microscope data that show that most nRt synapses are with relay cells not interneurons. Added complications are provided by two types of GABA receptors having differing effects, by different arrangements for the X and Y cells (see Sherman & Koch, 1990, for details), and by the fact that NB cells fire in two modes—rhythmic bursts and spike trains—so that their activity could either raise or lower the activity of their target cells depending on their mode of firing (Khateb, Mühlethaler, Alonso, Serafin, Mainville, & Jones, 1992). Moreover, ACh and GABA inhibit nRt neurons in different ways (McCormick & Prince, 1986). The latter inhibits all spike activity whereas the former inhibits spontaneous activity and produces short spike bursts. nRt neurons contain somatostatin as well as GABA. Steriade et al. (1990) suggest that the action of nRt neurons on thalamic relay neurons may be exerted by GABA in slow wave sleep (inhibition) and by somatostatin in the awake state (excitation).

A recent hypothesis (Liu et al., 1995) suggests a more subtle mechanism in which the nRt cells suppress background noise in the relay cells and so increase the signal-to-noise ratio, improving the faithfulness of the sensory relay (''noise'' here needs to be interpreted in the sophisticated sense we owe to Bullock [1993]; see also John [1979]). The nRt cells hyperpolarize the relay cells enough to inhibit random firing but not enough so as to cause inefficient burst firing by deinactivating the low threshold calcium conductance. Furthermore, spindling by nRt neurons inhibits transmission through the relay nuclei. Activation of NB inhibits this spindling (Buzsáki, Bickford, Ponomareff, Thal, Mandel, & Gage, 1988; Semba, 1991). In the case of action of NB neurons on target nRt neurons, as these are both active during the awake state, it seems unlikely that the former simply inhibit the latter: something more subtle may be indicated, possibly along the lines of the hypotheses suggested by Sherman and Koch (1990) or by Liu et al. (1995) for the action of nRt neurons on the relay cells. Another hypothesis (Newman, 1995) suggests that the action of nRt axons on thalamic relay neurons is not to act as a simple switch but to modulate ''high-frequency patterns of activation'' (≈40-Hz rhythms), thus facilitating the flow of relevant sensory information through the thalamus. This suggests that the nRt might have

more to do with the overall organization of ‘‘binding’’ than with selective attention per se.

Montero and Singer (1985, p. 164) say that the F1 terminals from nRt contacting the soma of the relay cells suggest ‘‘a powerful and global control of relay cell excitability.’’ They add that not enough is known yet about the detailed effects of interneuron activity to warrant speculation at this time on their functional significance. Suffice it to say that the nRt would appear to have a positive feedback effect on the thalamic relay nuclei based on complex circuits, the details of which remain to be elucidated.

The question has been raised by an anomyous reviewer whether there is any actual evidence to support Crick’s hypothesis. The anatomy of nRt precludes any ordinary lesion or stimulation studies related to behavior and there are no diseases that are confined to this nucleus. However, the detailed neuroanatomical and neurophysiological data reviewed in this section would seem to support Crick’s hypothesis (or some of the more recent models based on it, reviewed above). If nRt is not concerned with modulating the transfer of information through the specific nuclei of the thalamus (i.e., acting as the searchlight of attention, or at least as part of the control mechanism of the searchlight, even if this is confined to intramodal attention rather than intermodal attention), then what else could it be doing? One answer is to control synchronization of 40-Hz rhythms, but that in itself might affect attention as well as ‘‘binding.’’

Most of the nRt has a clear-cut topographic representation; that is, narrow slabs represent small primary cortical or retinal areas. These slabs lie parallel, not perpendicular, to the reticular sheet. The same arrangement is found relating to primary auditory, sensorimotor, and motor cortex. Exceptions are the ILN, which project diffusely to all regions of the nRt. The input clusters from the limbic system are not organized into slabs but fill the entire thickness of the nucleus. The limbic efferents from nRt go to anterior ventral, anterior dorsal, and lateral dorsal thalamic nuclei, all with limbic function. Input from secondary sensory cortex and the pulvinar are not arranged in slabs either. Input from the cingulate gyrus shows no slabs but has a loose topography (Lozsádi, 1994).

nRt cells are usually modular-specific except at junctions between areas. In addition to its connections to the rest of the thalamus and from the cortex, it has a complex chemical anatomy. There are dense specific neuropiles throughout the nucleus—noradrenergic from LC, GABAergic from the ventral pallidum and substantia nigra, GABAergic and cholinergic from NB, cholinergic from basal forebrain and brainstem (PPT and LDT), and serotonergic from the raphe nuclei (Asanuma, 1992). Shosaku, Kayama, Sumimoto, Sugitani, and Iwama (1989, p. 98) end their review of its function with the pithy statement that it is ‘‘primarily a tool of the cerebral cortex.’’

So this nucleus easily retains its candidature.

The Intralaminar Nuclei of the Thalamus

The intralaminar nuclei consist of an anterior group (central lateral, paracentral, and central medial) and a posterior group (centromedian, a.k.a. centre medián, and parafascicular).

The centromedian nucleus is a motor nucleus that relays signals between the globus

pallidus and motor cortex on the one hand and the sensorimotor striatal territory on the other.

The parafascicular nucleus connects with association and limbic cortex as well as the hypothalamus, PPT, and amygdala. It has an important projection to the subthalamic nucleus and to the striatum (to which the former has its major projection, thus constituting a thalamic–target–target triangular relationship). It also has a prominent input from the superior colliculus and the frontal eye fields (Sadikot, Parent, & François, 1992). It is particularly associated with pain (Coghill, Talbot, Evans, Meyer, Gjedde, Bushnell, & Duncan, 1994).

The lateral part of the ILN (central lateral and paracentral nuclei) projects densely to the neocortex and the neostriatum. Their main inputs come from the RF and deep cerebellar nuclei. This circuit conveys spinal and cerebellar inputs to the motor and parietal cortex (Su & Bentivoglio, 1990). It also forms the final common path for input from the RF to reach the cortex (Bogen, 1995a, 1995b; Newman, 1995).

Other inputs to the ILN come from NB (dense—Heckers, Geula, & Mesulam, 1992), raphe (dense—Lavoie & Parent, 1991) and, according to Royce, Bromley, and Gracco (1991), from every major division of the CNS. Other outputs go to the ventral striatum (n. accumbens and olfactory tubercule). More details about these projections are given by Bentivoglio, Minciacchi, Molinari, Granato, Spreafico, and Macchi (1988). The ILN do not receive significant input from the visual cortex (Koch, 1995).

Steriade, Corró Dossi, and Contreras (1993) state that the ILN distribute two major cortical rhythms, the 7- to 14-Hz sleep spindles and the 40-Hz rhythms typical of increased focal attention and motor preparation (Pfurtscheller, Neuper, & Kalcher, 1993). They are thus in a position to exert a powerful influence over cortical cells.

It used to be thought that the ILN projection to the cortex was nonspecific and diffuse. However, recent data show that these projections are fairly specific, with each nucleus in the complex making connection with specific parts of the cortex (see Berendse & Groenwegen, 1991; Fenelon, François, Percheron, & Yelnik, 1991, for details). The thalamocortical projection from the ILN uses glu/asp as its transmitter (Steriade, 1992; Steriade & Deschênes, 1988). The general level of arousal in the cortex is set by the rostral brain stem RF acting through the thalamic centrolateral and paracentral nuclei according to Steriade et al. (1990).

The functions of the ILN are often discussed within the framework of simple ''awareness,'' or ''cortical activation''—as a switch that turns parts of the cortex on and off. However, they may also subserve more subtle functions. Berendse and Groenwegen (1991) suggest that thalamic relay nuclei deal with the discriminatory aspects of sensation and that the ILN/midline nuclei (or at least the parafascicular nucleus) deal with the affective component required in particular by the organism to detect new and potentially dangerous situations. The specific relay nuclei project to cortex and only sparsely to the striatum. The ILN project to both. The affective information to the striatum from the ILN can either prepare the striatum for an imminent cortical input or, in certain circumstances, induce a ''timely first behavioral response'' that can later be modified by cortical input. Watson, Valenstein, and Heilman (1981) likewise suggest that the ILN prepare the organism to respond appropriately to a meaningful stimulus. The projection of the ILN to the striatum is part of a circuit

that leads to the substantia nigra pars reticulata and then to the superior colliculus before returning to the ILN. Different populations of cells in the superior colliculus mediate two different types of behavior: (i) escape/avoidance via the parafascicular nucleus and (ii) orienting/approach via the central lateral and paracentral nuclei (Grunwerg & Krauthamer, 1992).

Bilateral lesions of the ILN lead not to coma but to akinetic mutism, which is regarded by some as representing a bilateral neglect syndrome. Bogen (1995a) states that bilateral lesions of the ILN lead to coma and therefore the ILN may form the key locus in the brain to support conscious awareness. However, my reading of all the clinical literature he quotes and other sources indicates that, following a bilateral medial thalamic stroke, loss of consciousness may certainly occur but this very rarely lasts more than 48 h. This is followed by akinetic mutism (''coma vigil'') or a fluctuating state of hypersomnolence plus amnestic problems due to damage to the mamillothalamic tract. Unilateral lesions of the ILN lead to contralateral unineglect in primates and humans (Colby, 1991; Watson et al., 1981). A patient reported by Watson et al. (1981) with a right medial thalamic infarct showed transient trimodal (auditory, visual, somatosensory) hemineglect. The syndrome can also result from lesions of the midbrain reticular formation (Watson, Heilman, Moller, & King, 1974) and of the putamen (Heir, Davis, Richardson, & Mohr, 1977). Neglect is a most complex phenomenon, recently reviewed by Ramachandran (1995), crucially important for our understanding of awareness (see also Cubelli, Nichelli, Bonito, De Tanti, & Inzaghi, 1991). In many cases neglect does not represent so much a failure of sensory *at*tention but of motor *in*tention (Watson, Miller, & Heilman, 1978). In either case, neglect, either unilateral or bilateral, is not to be equated with loss of consciousness.

Akinetic mutism is a peculiar condition in which purely passive ''awareness'' seems to be maintained. The patient remains aware of what is going on but is unable to, and does not even want to, respond or communicate (Crick, 1994). Thus what Crick calls the ''will'' (or active awareness) seems to have vanished. There are two types of akinetic mutism: ''vigilant'' and ''somnolent'' (Segarra, 1970). The former is associated with lesions of the cingulate cortex and the medial forebrain bundle, the latter with lesions of the midbrain tegmental area. Recent data indicate that dopaminergic projections are involved. Cases of akinetic mutism respond well to dopaminergic agonists such as bromocriptine (Echiverri, Tatum, Merens, & Coker, 1988; Ross & Stewart, 1981). A similar syndrome can be produced in animals by 6-OH DA injections into the substantia nigra, ventral tegmental area, or the medial forebrain bundle. These syndromes are all reversed by bromocriptine but not by L-DOPA or by methyphenidate (cholinergic). However, one case is reported in the literature of akinetic mutism that followed damage to the RF in the region of the ventral end of the aqueduct, which responded to methylphenidate (Daly & Love, 1958), suggesting a cholinergic component. In another case the lesion was confined to the dorsal thalamus (MD, anterior nucleus, ventrolateral nucleus, and pulvinar, sparing the ILN, midline nuclei, and the tegmentum) (Segarra, 1970). Another case of terminal renal failure developed a state of akinetic mutism following a single dose of the GABAergic derivative baclofen (Parmar, 1991). Akinetic mutism can also be a complication of hydrocephaly when there are repeated shunt failures leading to damage to dopaminergic fibers in the median forebrain bundle (Anderson, 1992). It can also result

from necrotizing leucoencephalopathy (Gütling, Landis, & Kleihues, 1992). This produces bilateral lesions confined to the white matter that cut connections between the thalamus and the reticular formation with frontal regions, in particular the cingulate gyrus.

Possibly the difference between vigilant and somnolent akinetic mutism may be due to damage to other sleep-related structures in the tegmentum in the case of the latter. Lesions confined to the periaqueductal gray do not lead to akinetic mutism but to euphoria (Segarra, 1970). During slow wave sleep the ILN are inactive; during REM and waking they are active. The connections of the ILN with the olfactory system are unclear.

The ILN seem therefore to be a key part of the anterior ''motor'' intention system, in which case they are unlikely to play the role of ''binding'' sensory information together allotted to them by Llinás and Paré (1991). Nor do they appear to play the role as chief mediator of conscious awareness allotted to them by Bogen (1995a, 1995b), for reasons given above and by Koch (1995). Clearly these nuclei have a close connection with motor ''intention'' but possibly a less close connection with sensory ''awareness.'' However, it seems clear that the different subdivisions of the ILN have very different anatomical connections and this suggests they are doing different things. So no theory of *the* function of the ILN would seem justified.

The Dorsomedial Nucleus of the Thalamus

This nucleus is divided into three segments—medial, central, and lateral (most of the neuroanatomical data unfortunately comes from the rat) (Benjamin & Jackson, 1974). The input to the medial segment comes mainly from many limbic areas. It also has two-way connections with prelimbic, cingulate, and insular cortex. The central division has mainly an olfactory input from the pyriform cortex as well as input from the lateral hypothalamus, lateral preoptic area, and the diagonal band of Broca. Its two-way cortical connections are with lateral orbital prefrontal cortex and the ventral insular cortex (both secondary olfactory cortex).

The lateral segment has input from the superior colliculus, lateral dorsal nucleus of the thalamus (limbic), substantia nigra pars reticulata, globus pallidus and LDT, and the interpeduncular nucleus. It has two-way connections with the dorso-lateral cingulate cortex.

All segments receive input from the nRt, PPT and LDT, raphe, LC, and the RF. Ray and Price (1993) describe how the medial segment of MD forms a triangular circuit between the limbic system and the cortex. The former projects partly directly to the latter and partly indirectly via MD. The cells in the limbic amygdala that project directly to the cortex are large, sparse, and with long dendrites. The cells that project via MD are small, dense, and with short dendrites. Ray and Price (1993) suggest that the former alert the cortex (''important message coming'') whereas the latter carry detailed information. The ventral pallidum (n. accumbens and the substantia nigra pars reticulata) does not project directly to the cortex but only via an inhibitory GABAergic pathway to MD. Different parts of MD take part in four of the five cortico-striatal-thalamocortical loops described by Alexander, DeLong, and Strick (1986)—the oculomotor; dorsolateral prefrontal (spatial memory); lateral orbitofron-

tal (switches in behavioral set); and the anterior cingulate (limbic). These loops link one specific area of the cortex (with some input from other areas of cortex) to specific regions of the striatum, then to specific regions of the pallidum and substantia nigra then to local areas of MD, and finally back to the original specific cortical area. The fifth motor loop uses the ventrolateral nucleus and not MD. Each of these major parallel circuits is probably made up of many minor circuits, each responsible for different parameters.

Ray and Price (1992, 1993) suggest the following functional anatomy of this system. The basis of sustained delay-related behavior may depend on reverberating cortico-thalamo-cortical loops. In orbital and medial prefrontal cortex this reverberation is facilitated by simultaneous excitatory inputs from the amygdala and other parts of the basal forebrain to both cortex and thalamus. The GABAergic input to MD from the ventral pallidum inhibits this reverberation. Excitation of MD is needed for sustained concentration (attention) on a particular task. Inhibition of MD may be necessary to block this before attention can switch to some different pattern of activity or to suppress unwanted thoughts and feelings. Thus reverberatory activity in cortico-thalamic-cortical circuits must be blocked temporarily by inhibitory pallidal input in order to allow new patterns to be initiated. The pallidomotor projection system suppresses unwanted activity in antagonist muscle groups. The pallidothalamic input may play a similar role in cognitive and affective function. Lesions of the MD nucleus in primates lead to severe memory disturbances (Heckers et al., 1992) and motor perseveration (Ray & Price, 1992). Lesion experiments in rats show that the memory disturbance is not the anterograde amnesia that results from hippocampal damage but an interference with the process of encoding new information into memory (Winocur, 1990).

Lesions of the subthalamic area cause gross disturbances in intention. The subthalamic nucleus carries the major excitatory input to the pallidum involved in the selection of motor behaviors. The neocortex (with the cerebellum) initiates and combines motor programs. The basal ganglia act in parallel to enable the selected program and inhibit potentially competing programs (Mink & Thach, 1993). A similar system may operate for the ventral pallidum and MD in connection with cognitive tasks.

Further cases of MD lesions (surgical thalamotomy) leading to an altered time sense are reported by Spiegal, Wycis, Orchinik, and Freed (1956). They describe a syndrome they call ‘‘thalamic chronotaxis,’’ which involves disorientation in time (not due merely to a defective memory). It involves a change in ‘‘time sense’’ and the patients report a feeling that they are much younger, and that all time intervals are shorter, than they really are.

Lesions of the ‘‘paramedian thalamus’’ cause ‘‘utilization behavior’’ (Eslinger, Warner, Grattan, & Easton, 1991). This starts with excessive drowsiness, with slow and sharp waves in the anterior EEG. Then the patient becomes unable to inhibit utilizing objects around her and will pick up and use appropriately objects in her vicinity, peel oranges, unlock padlocks, spend all day making and unmaking her bed, and so on. Tests show a great decrease in concentration and in focusing, maintaining, and shifting attention, together with disorientation in time and space. A similar syndrome can follow frontal (particularly orbito-frontal) lesions (Lhermitte, 1983; Shallice, Burgess, Schon, & Baxter, 1989). The syndrome seems to be due to discon-

nection between the parietal and the frontal lobes so that the many subprograms operated by the former in response to numerous environmental stimuli are not inhibited, when inappropriate, by the latter acting as a ''supervisory attentional system.'' Presumably some paramedian thalamic nucleus (possibly MD), rather than direct connections between the frontal and parietal cortices, mediates, or is essential for, this function.

Thus the dorsomedial nucleus must also be regarded as a key player in the attention/intention circuits.

Other Systems

The LC and raphe (plus histamine) certainly play a major role in the sleep–wake cycle. The LC contributes to the control of focused attention. Expectancy behavior is inhibited by the LC. During waking the LC and raphe are both active but in REM sleep they are inactive. As we are certainly ''aware'' during dreams, this indicates that these systems, although they may modulate attention, are unlikely to be responsible for primary awareness.

Dopaminergic mechanisms based on the tegmentum, besides contributing to the control of focused attention behavior and reinforcement mechanisms, also seem to play a role in ''active'' attention (the ''will'') as the data from akinetic mutism indicate. These of course may represent different aspects of the same mechanism. The dopaminergic A 10 neurons are involved in cognition and play a role in spatial learning, memory, and reward mechanisms among others (Gasbarri, Packard, Campana, & Pacitti, 1994).

Thalamic Enhancement Circuits

Thalamic nuclei often show triangular relationships between two brain areas that project to each other. La Berge (1990) has suggested a functional reason for this related to selective attention. In his system (for vision) he recognizes a Feature Register (V1), which registers a stimulus array, say H O H. This projects to the Shape Register (in this case in the occipito-temporal cortex), for which only the O is wanted. In between, in a triangular relationship, he places the Filter, which gets rid of the two H's by lateral inhibition. For vision the Filter is the pulvinar. The Filter must have a topographic map of the Feature Register contents as well as an algorithm for lateral inhibition. He sees attention as having two essential components (i) *selective,* which inhibits competitors and boosts the target activity, and (ii) *expectation,* which leads to more efficient processing of the target. Higher-order processes select a particular cortical area and prepare it for the expected information to arrive and they then direct the pulvinar (for vision) to shunt information to the selected cortical locus. In this way La Berge sees thalamic circuitry, using these Thalamic Enhancement Circuits, as magnifying small differences between rival cortical circuits very quickly. In other systems these triangular circuits may subserve a similar function. He suggests, for example, that MD operates a Thalamic Enhancement Circuit for comprehension.

Another basic mode of operation of triangular circuits has been emphasized by Freeman (1994). He sees the brain operating largely according to principles of nonlin-

ear chaotic dynamics. When one such brain activity pattern expresses a drive toward a certain goal, its effects bifurcate. One set goes to the motor system. The second goes to all sensory areas to prepare them for the impending changes in sensory input that will follow the motor action. Feedback from these return to the central system to ensure that the operation has been carried out correctly. Neuroanatomical candidates for this function could be the ILN or the pallidum-MD system.

DISCUSSION

Anyone trying to make sense out of the functional anatomy of the brain soon develops the feeling that everything connects to everything else in circuits of bewildering complexity and that Dennett, after all, must be right and the brain is completely nonlinear. Clearly key brain functions are distributed widely in complex networks that spread over diverse neuroanatomical areas. At the same time there is clear evidence that different parts of the cortex and related subcortical structures are specialized to process different information and exert different functions. But is it possible to say anything more than that with respect to the functional neuroanatomy of awareness and attention?

A model of some of the functional neuroanatomy of the awareness system might run as follows: A lower-level intramodal control of the ''spotlight of attention'' is carried out by nRt as in Crick's original hypothesis. Finer grained changes might be determined by competing cortical dominant foci or ''small flashlights.'' However, it remains unclear whether the input from nRt to the specific thalamic relay nuclei opens or shuts the gate (La Berge 1990; Montero & Singer 1985; Ohara et al., 1980; Steriade et al., 1986). On functional grounds the former seems the most likely. The hypotheses that best fit the data would seem to be those of Sherman and Koch (1990), Liu et al. (1995), and Newman (1995), as detailed earlier.

The nRt may be subject to ''higher'' modulatory control by the chemospecific inputs: (1) GABA and ACh from NB, which in turn is subject to control by the topographically organized input from the cortex. This circuit may allow input of the significance of stimuli. Firing of NB neurons rises in response to significant stimuli and NB neurons are quiet during slow wave sleep (Metherate & Ashe, 1993). The inferior parietal lobule may also be concerned with determining what is important in the stimulus input (Watson & Heilman, 1979); (2) norepinephrine (locus coerulus); (3) serotonin (raphe); (4) dopamine (ventral tegmental area); and probably many others (e.g., histamine, and innumerable polypeptides).

A diffuse, widespread release of, say, NE might signal ''Whatever you are doing now continue as reinforcement has been received'' (see Smythies, 1970) but it is difficult to see how this could signal ''Attend to that little spot down to the left'' when the brain mechanisms work out that the little spot, causing by itself a minimum signal to nRt, is meaningful (e.g., seeing a five-dollar bill on the ground). A diffuse release of the appropriate ''labeling'' neurotransmitter in nRt would presumably label everything going through nRt, little spot and everything else included. Asanuma (1989) proposes that NB can ''strategically modulate'' the excitability of nRt neurons and so affect the initial transmission of information to the cortex, to which nRt has its major projection in a triangular relationship. However, what may be important

for awareness is not the mere transmission of impulses but the synchronization of their oscillations. Perhaps a diffuse projection (e.g., from all these chemospecific nuclei to nRt) is suitable for that. Moreover it is important to distinguish between the mechanisms that provide the *content* of consciousness at any one moment (i.e., selected hierarchically organized activity in cortex, thalamus, and cortico-thalamic loops, plus possibly loops connecting the olfactory bulb and the pyriform cortex) and the switching intermodal *attention* mechanisms that do the selection (which include but are not confined to the PPT and LDT on the attention side and the ILN and pallidum-MD on the intention side). ''Selection'' here is used in the sense familiar to users of word processors.

This model of the cortex–nRt–relay nuclei–cortex loop is reminiscent of the double inhibitory motor striato–pallidal–thalamic system. Here, lateral inhibition in the striatum deletes unwanted motor patterns in adjacent striatal neurons. In the attentional system this lateral inhibition could be effected by the extensive local GABAergic inhibitory circuits set up by the axon collaterals of nRt cells (De Curtis, Spreafico, Panzica, & Avanzini, 1988) as well as the type of circuits in the relay nuclei postulated by Sherman and Koch, if present (1986).

The intentional system (Crick's ''will'') may depend in particular on circuits based (a) on the ILN and cingulate gyrus that link the frontal and parietal lobes, and (b) on the loop that runs from the cortex–ventral striatum–ventral pallidum–lateral MD– and back to the cortex (particularly cingulate cortex), plus input from the dopaminergic ventral tegmental area to the ventral pallidal part of this link. The source of lateral inhibition in this circuit may be the ventral striatum.

Kinomura, Larsson, Gulyás, and Roland (1996), in a PET study of normal humans, found that the change from a relaxed awake state to an attention-demanding reaction-time task was accompanied by activation of the midbrain RF and the ILN, especially the centro-median and lateral central nuclei. But this did not happen when the volunteers simply pressed the button when they wanted to. Possibly the centro-median nucleus mediates some aspect of attention–intention linkage and the central lateral nucleus acts as the relay signal from the midbrain RF to the cortex.

The question remains as to what keeps the two systems—attention and intention—in synchrony? Since the middle layer of subcortical structures seems to belong firmly to one or the other, the answer might be either very low down (?RF) or very high up (cortex). Alternatively there might be significant cross-talk among key elements of the system, for example along the projections between the ILN and the lateral ventral and anteroventral thalamic complex and nRt, and circuits involving the insula.

As Crick has urged, there is clearly a need for further clinical investigations in this area, in particular into the questions of whether human cases of temporal and frontal lobectomy are really *aware* of olfactory stimuli with normal detection thresholds, what the experience of someone with akinetic mutism is really like, further studies of thalamic pain, what type of blindness results from lesions of the optic radiations, and hierarchical aspects of awareness in different conditions.

In conclusion, a good case can be made for the hypothesis that, whereas the five systems I delineated above, as well as nRt, that are concerned with awareness and intention, clearly form an orchestra, as Crick (1984) suggested, the conductor of the orchestra may well be PPT and LGT, which constitute a major part of the cholinergic

system in partnership with the cortex, together possibly with other nuclei in the adjacent mesencephalic (or lower) RF whose neurochemistry has not yet been determined (Steriade, 1992). The insula seems to play a key role in the conscious appreciation of pain.

It may be thought strange that such small nuclei could have such major effects: Descartes put the pineal gland in this role, and these nuclei are much smaller than that! However, as Baars (1995) points out, surprisingly small subcortical structures may be needed for the *state* of waking consciousness, whereas the much larger thalamocorticothalamic circuits seem to provide the *content* of perceptual consciousness.

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