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Group Report
The Integrative Function of the Neocortex

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SCOPE AND ORGANIZATION OF DISCUSSIONS

The other groups at this conference have dealt with questions about the implementation of intracortical functions in terms of the anatomic and physiologic characteristics of synapses, local circuits, the mapping of particular functions, laminar arrangements, and plasticity. The task before our group was to address issues concerned with the "integration" of these mechanisms and of the information processed in cortex. There are obviously a large number of topics that could have been addressed within the scope of this inquiry, and it was necessary to generate an organizational framework and selected list of topics that could be reasonably dealt with in the time allotted and with the expertise of the attendees. Thus, the subsequent discussions were organized around five major problem areas which are described below.

Initially, however, it was necessary to provide an operational definition for the topic of integration so that discussions could hopefully be focused on what we agreed to be promising areas for near-term study. The consensus was that the most general statement of the problem to be addressed by the group was how cortical information, once analyzed,was reunified into larger chunks such as "percepts," "intentions," and behavioral responses. In general, these integrative processes are believed to be accomplished through interactions at the cellular, cell ensemble, areal, and regional levels within the neocortex. These cortical processes are facilitated by subcortical structures which provide cortical "activation" or "implementation." Somehow behavioral state changes are induced in cortical structures; somehow cortical

information is transcribed into meaningful code for subcortical motor structures; somehow new input arriving at the cortex is attended to selectively or compared with previous information. These integrative processes were selected as examples that could be dealt with in some detail and with some expertise by the group. Finally, it was clear that these processes may take different forms depending on the developmental stage of the organism, experimental manipulations, or other conditions, either natural or imposed, that would alter the characteristics of these operations. Each of the five discussion sections focused on a major question about cortical integration, specifically:

1) What is the role of "nonspecific activating" systems in cortical function?
2) How can we relate the behavioral phenomena of selective attention to single neurons, neuronal assemblies, and neuronal systems in the cortex?
3) How can we relate single-unit activity to perception, to the development of perception, and to perceptual disorders after brain damage?
4) How do we assess the dynamics of cortical mechanisms underlying human cortical function?
5) Coordinate transformations: How are spatial coordinates transformed into appropriate motor commands?

WHAT IS THE ROLE OF "NONSPECIFIC ACTIVATING" SYSTEMS IN CORTICAL FUNCTION?

It is well known that in addition to the major sensory and motor systems which provide input to the neocortex, there are afferents which originate in thalamic and nonthalamic cell groups which appear to mediate the changes in cortical activity that accompany changes in behavioral state, such as the sleep-wake cycle and arousal (see Bloom, this volume). The importance of the cortical "tonus" supplied by such input was first demonstrated by Moruzzi and Magoun (1949) with the observation that stimulation of the brainstem reticular formation resulted in EEG desynchronization. It was long thought that the cortical activation resulting from such stimulation and its disruption following reticular core lesions could be accounted for by a unitary reticular activating core. More recently, the availability of transmitter-specific anatomic methods and sensitive tract-tracing methods has produced a new conceptualization, that of a differentiated, transmitter-multiplexed, coordinated complex of ascending activating systems. At the present time, the cellular mechanisms by which these major afferent systems impose particular changes on the neocortex are not understood. Six of these systems are composed of brainstem neurons which project monosynaptically onto wide regions of the neocortex. These are the locus coeruleus-noradrenergic system, the raphe-serotonergic system, the substantia nigra-ventral tegmental area-dopaminergic system, the nucleus basalis-cholinergic system, and more

recently characterized systems of presumed histamine- and GABA-containing neurons which reside in the hypothalamus. Although these groups are superficially similar in organization, arising from numerically limited brainstem and basal forebrain populations and projecting widely through neocortex, detailed studies have revealed striking differences between them. For example, each system has a unique pattern of regional and laminar projections into neocortex, a differentiated intrinsic and topographic organization, and specialized discharge properties of source neurons. In addition to these six systems, there are two "arousal" systems which originate in the brainstem and project into the thalamus. One of these projects from midbrain tegmental areas onto intrathalamic cell groups which, in turn, project broadly into the superficial layers of neocortex where they are thought to alter the general responsivity of neocortex. The other system of this type originates from reticular formation groups and projects to the nucleus reticularis of the thalamus where it presumably exerts a strong influence on the mode of thalamic activity, helping to impose those changes in thalamocortical discharge patterns that characteristically accompany the state changes of the sleep-wake cycle.

In general (with certain exceptions noted below and others in the literature), these systems have been characterized anatomically at the light-microscopic level for certain species and for certain cortical regions, and there is some information about the physiological characteristics of source neurons and the physiological impact of the putatitve neurotransmitter on postsynaptic elements in cortex and/or thalamus. Some of the effects of lesioning of these systems are also known. However, there are crucial areas of ignorance. For example, for most cortical regions, for most of these systems, and for most species, the class(es) of cortical neurons which receive input from a given system is unknown. In some cases, the effect(s) of the putative transmitter on the conductances present in the postsynaptic cortical neuron has not been characterized, at least *in vivo*. Also, the effects of the transmitter, released physiologically, on the functional sensory-elicited activity of cortical neurons have been characterized in very few cases. Finally, the ultimate demonstration that a particular system is a necessary and/or sufficient agent for the induction of physiologically occurring changes in the operating characteristics of a particular cortical network has not been evaluated in a rigorous fashion for any particular system. Despite these severe limitations on current knowledge, there are circumscribed islands of knowledge which offer reason for optimism in ultimately delineating the cellular characteristics of these systems and understanding their physiological functions. Some of these data were discussed at this session.

At the anatomic level some of the most detailed ultrastructural studies have been conducted on the cholinergic projection into cortical area 17. Immunocytochemically labeled synapses have been observed on all three of

the cell types that can be directly identified in ultrastructural material (i.e., pyramidal, spiny stellate, and aspiny stellate). These synapses appear mostly on dendritic shafts and in the superficial layers. Singer speculated that these cholinergic inputs may alter the mode of firing of cortical neurons in a manner that has been observed during sleep-wake transitions. He also summarized data from his laboratory in which the facilitatory effects of reticular-formation stimulation on visual cortical responses have been determined. In these experiments it was found that such facilitation will persist even if the intralaminar complex, basal forebrain cholinergic neurons, or ascending noradrenergic projections are lesioned. However, limited lesions in the cingulate cortex will abolish the reticular formation-induced facilitation. These results indicate that the ascending systems from the reticular formation are robust and redundant and that there may well be interactions between these systems so that they reinforce effects induced by the other. At the present time, the mechanisms of such interactions are unclear, although the anatomic bases for interactions between certain of these systems are known to exist. These observations also raise the question of the extent to which these systems are mutually reinforcing, or, perhaps, act antagonistically, some balancing the effects of others.

Merzenich presented new data which might reflect the physiologically induced operation of one or more of the activating systems. In the experiment he described, peripheral nerve stimulation in an anesthetized rat was found to induce large changes in the sizes of cortical receptive fields for individual vibrissae. The effect was found to be naloxone reversible, suggesting that it might be mediated by an activating system, at least one link of which is an opioid synapse.

A question was raised about the nature of the deficits in cortical function that have been demonstrated following lesion or pharmacological manipulation of one or more of the ascending activating systems. Several examples were offered. There is the common observation that scopolamine alters the electrophysiological activity of neocortex, induces behavioral electrographic dissociations, and leads to memory deficits. There have been suggestions that the noradrenergic system, or the noradrenergic plus the cholinergic systems are essential for certain types of cortical development plasticity, especially ocular dominance shifts following monocular occlusion. There has been a demonstration that dopamine depletion in frontal lobes of monkeys induces a deficit on delayed response tasks that is as severe as that observed if there is removal of a substantial portion of prefrontal cortex. Also, administration of the adrenergic agonist clonidine has been shown to reduce cognitive deficits in aged monkeys that appear to result from the compromised function of the frontal lobes.

Prince described the characteristics of a number of voltage and transmitter-sensitive conductances that can be studied *in vitro* in the cortical slice (see

Prince, this volume). For example, he described three distinct effects of acetylcholine (ACh). This transmitter affects pyramidal cells via M1 receptors, the net effect being to enhance the responses of these neurons to prolonged activating inputs. Second, distinct effects of this transmitter are also evident on GABA interneurons and, third, on presynaptic terminals. These observations prompted two immediate questions: which of these phenomena are physiologically operative *in vivo* and why are there three distinct effects of this transmitter in cortex? Could it be that each of these effects results from the activation of a distinct set of cholinergic afferents which could be separately controlled? Prince then pointed out an additional element of complexity in this picture: the observation of still other cholinergic effects at the thalamic level. One effect is exerted on neurons of the nucleus reticularis thalami. Application of a moderate amount of ACh hyperpolarizes the membrane by activating a potassium conductance and switches the discharge of these cells from a single-spike mode into a bursting mode because of activation of the low-threshold calcium spike. Further membrane hyperpolarization by ACh might lead to a complete cessation of activity in these neurons. Since these cells play a major role in "gating" thalamic relay neurons, presumably by recurrent inhibitory collaterals, release of this transmitter onto these neurons might have the net effect of activating the thalamic input to neocortex. ACh also has direct excitatory actions on thalamocortical relay cells in LGN where it produces, among other actions, a slow depolarization by decreasing a potassium conductance. These actions would be compatible with the activating effects of ACh on neocortex itself. Prince pointed out, however, that there may be substantial species differences in some of these phenomena, which make much more detailed study necessary. Finally, he noted that norepinephrine and ACh effects on hippocampal pyramidal cells are mutually reinforcing in that each transmitter reduces a Ca^{2+}-mediated K^+ conductance, thereby reducing the afterhyperpolarization which results from a sustained activation of the cell. Corticotropin-releasing factor is also known to induce this effect, which serves to make the cell more responsive to sustained, strong excitatory drive.

There were comments from Sillito and Singer reinforcing the concept that ACh has appropriate anatomical localization and physiological effects to serve as an activating agent in the visual system at both the thalamic and the cortical level. Lamour reported that the iontophoresis of ACh onto cortical SMI neurons in the rat produced threshold changes in the receptive fields of about 35% of the neurons studied (Lamour et al. 1983). Furthermore, in some cases these changes were observed for long periods of time. This is compatible with previous *in vivo* observations by Woody indicating that this transmitter can have prolonged effects (Woody et al. 1978). It was also noted that whereas the monoaminergic systems appear to have inhibitory recurrent collateral arrangements, the application of ACh to nucleus basalis

neurons activates them, indicating that these neurons may be partially driven by mutual facilitatory interactions (Lamour et al. 1986).

SELECTIVE ATTENTION: HOW CAN WE RELATE THE BEHAVIORAL PHENOMENA OF SELECTIVE ATTENTION TO SINGLE NEURONS, NEURONAL ASSEMBLIES, AND NEURONAL SYSTEMS IN THE CORTEX?

Selective attention is observed at the behavioral level when the organism, by intrinsic mechanisms, becomes more responsive to certain aspects of the environment and diminishes its responsiveness to other aspects of the environment. These processes operate both between and within sensory modalities. Responsiveness to stimuli in one sensory modality can be selectively enhanced at the cost of decreased sensitivity in other sensory modalities. Within a sensory modality, selective attention can occur between different channels (e.g., attention to auditory stimuli delivered through one ear vs. those delivered through the other ear), between particular stimulus characteristics or features, and between particular portions of extrapersonal space. This last type of selective attention is currently the focus of intensive study, especially in the visual modality, both at the organismic level and at the level of individual neurons. Behaviorally, there is clear evidence that there can be enhanced responsiveness to, and detectability of, stimuli presented at particular points in space when the subject is previously informed to attend to that spatial region. This advanced cueing can substantially reduce processing time in numerous tasks. These observations imply that brain mechanisms exist which can alter the operating characteristics of sensory processing machinery in a space-dependent fashion. In such paradigms, there is inevitably a decrease in processing efficiency and/or sensitivity in other portions of extrapersonal space. These costs may be especially profound in the hemifield which does not contain the focus of attention. Major questions which arise as the result of such phenomena are whether this enhanced reliability and efficiency of performance is due to enhanced sensory processing, or whether it reflects the operation of some premotor facilitation. Does such activation reflect very general processes or some highly specific mechanism (s)? At the behavioral level, these facilitatory processes often possess a high degree of spatial selectivity. If a general activating system underlies these phenomena, this high degree of spatial localization must be explained by some interactive mechanisms which have not yet been specified. From the plethora of behavioral data which are available, it is clear that there are probably several attentional mechanisms, with different latencies and specificities, that must be operative under selected circumstances. In certain human paradigms, for example, some

general facilitation is evident within 40–50 ms of cueing, and this facilitation becomes more enhanced and more focused over the next 50–80 ms.

Goldberg and others (see Goldberg and Bruce 1985) have shown that there are neurons in the parietal lobe of the monkey which show an enhanced response to visual stimuli presented in their receptive field when the locus of the receptive field is specifically attended to by the monkey. This enhancement effect is similar to that first shown in superior colliculus by Goldberg and Wurtz (1972). Mountcastle described a different example of the effects of selective attention on parietal cortex neurons in the freely behaving monkey. He described neurons which show enhanced responsiveness in extrafoveal portions of the receptive field when the animal selectively attends to the foveal region. This effect is paradoxical in that such neurons become more sensitive to stimuli occurring outside the focus of attention. The biological significance of this effect may be that of counteracting the costs for the peripheral visual field of directing attention to the fovea, thus keeping some degree of responsiveness throughout the visual field. In addition, this effect could enhance ambient vision during forward motion. This phenomenon is not observed in V1 or V4. The question was posed whether this phenomenon could be mediated by intralaminar, pulvinar, or central core mechanisms. Allman suggested that area PO in rhesus monkey (analogous to area M in owl monkey), an area selectively responsive to peripheral stimuli (Allman et al. 1985; Baker et al. 1981), might be responsible for activating peripheral responses in other visual areas. He also noted that he has observed fluctuations in the response properties of V1 cells as experimental contingencies are changed and suggested that there might be some types of attentional mechanisms operative in this cortical region. Creutzfeldt quoted evidence from B. Fischer (Fischer et al. 1981; Boch and Fischer 1983) which documents a strong and specific involvement of neurons in V4 in attentional processes. Such neurons not only respond in connection with visually elicited saccades, their responsiveness to visual stimuli strongly depends on whether a stimulus should be attended to or not.

A major question which was discussed at length was an expanded version of these issues. Are there very general, subcortically mediated selective attentional processes as well as cortically mediated, highly focused selective attentional processes? The viewpoint that there may be no low-level, general gating processes was voiced. For example, there are evoked potential data which indicate that certain types of selective attention can be elicited by stimulus features that require substantial processing, and thus the attentional process must occur after sensory processing. The point of view that there may be general activation or attention processes which lack selectivity, but are a prerequisite for selective attention, gained a general consensus. This view emphasized the importance of low-level attentive processes but also

emphasized the requirement of cortical mechanisms for highly selective attentional phenomena.

The next focus of discussion was whether there might be brain structures dedicated to attentional processes or whether these processes were an integral part of sensory-motor machinery. Rizzolatti discussed hemi-neglect as a syndrome that is useful in approaching this question. Hemi-neglect can be elicited by lesions in parietal, frontal, and cingulate as well as other areas. This has led to the proposal that there is an "attention circuit" which includes these areas. In these particular experiments, monkeys received lesions in the area of the frontal eye fields. Clear deficiencies of eye movements and attention were observed. However, when a postarcuate area was destroyed, the expected motor deficit was observed, and there was hemi-neglect only in "close" extrapersonal space (or peripersonal space). Rizzolatti's interpretation of these data was that the hemi-neglect thus reflects the domain of the motor deficit and that neglect is probably a reflection of interfering with sensorimotor processing rather than with an attentional process per se. This would explain the distributed areas from which neglect can be elicited. However, it was noted that bilateral prefrontal lesions in several species have been shown to exaggerate certain attentional processes, often in a stimulus-bound fashion.

The question of the brain level which is responsible for certain attentional processes was further discussed in light of data from split-brain patients. Gazzaniga summarized these data as indicating that the operation separates the sensory processing and motor mechanisms of the two hemispheres but that attention seems to often retain its unitary or bihemispheric nature. The data support the view that attentional phenomena often reflect the operation of a brain system that is independent of perceptual and motor processes. For example, certain types of spatially directed attention transfer across the midline, such that spatial cues presented to one hemisphere can serve to focus attention in the other hemisphere or to direct eye movements to the opposite hemifield. A non-split patient with unilateral occipital damage did not exhibit these effects, thus indicating that integrity of the cortical-collicular pathways is essential for such transfer. Gazzaniga interpreted these results to indicate that there is a global and subcortical nature to certain attentional processes (see Gazzaniga, this volume). The consensus of the group was that many systems at the cortico-to-subcortical, brainstem-to-cortex, thalamus-to-cortex, and corticocortical level are involved in attention. It was agreed that another major outstanding question was the extent to which interactions between "nonspecific activating" and "specific thalamocortical" systems could yield attentional mechanisms with localized impact (see Bloom, this volume).

What types of experiments would provide crucial information for resolving these outstanding major questions? It was agreed that careful examination

of the latencies of these activating or facilitating processes would provide important information about what their neural mechanisms might be. Careful utilization of event-related potential data from both humans and animals might be especially useful since there are particular components (e.g., N1) which are sensitive indices of attentional processes. There was disagreement about whether certain scanning techniques, such as PET, might possess sufficient temporal or spatial resolution to directly address these questions. Many felt that animal experiments, which would permit single-cell electrophysiology, lesions, and activation of certain neural structures, were more important to pursue than more refined human experimentation. These would permit experimenters to directly address the criteria of necessity and sufficiency for the roles of particular neural substrates in the occurrence of these phenomena at the behavioral and neurophysiological levels. There was a consensus that recordings from source neurons for brainstem activating systems during defined variations in focused attention would be very helpful.

Van Essen and Allman (personal communication) presented recent human data obtained using PET-scan methods. Currently, the resolution of the method is limited to a few millimeters, and it is possible to do up to eight determinations in a single subject in a single sitting. PET data are collected for an interval of 40 seconds. In the experiments now being performed, a PET scan is performed, then an MRI scan, and the PET results are mapped onto the MRI image which currently has a 2-point resolution of 0.5 mm. The MRI image can then be unfolded. The initial experiment involved mapping area 17 where it was possible to detect two points separated by 5 mm on the cortical surface and 1.5° in the visual field.

PERCEPTION: HOW CAN WE RELATE SINGLE UNIT ACTIVITY TO PERCEPTION, TO THE DEVELOPMENT OF PERCEPTION, AND TO PERCEPTUAL DISORDERS AFTER BRAIN DAMAGE?

If the brain utilizes individual neurons to extract features of the visual world, how is this information reintegrated into the phenomena of perception? This issue was initially addressed by a discussion of the properties of visual neurons in the temporal lobe.

Gross presented a summary of what is currently known about the response characteristics of inferior temporal lobe visual neurons. He began by noting that lesions in this area produce a deficit in visual recognition and learning, that this deficit is restricted to the visual modality, and that there is no loss of visual acuity or changes in other psychophysical thresholds. He, and others subsequently, have observed that neurons in this area are in fact driven by visual stimuli and that their properties are substantially different from neurons in other visual areas (see Gross 1972; Mishkin 1972). The

receptive fields are large and nontopographically organized. Their integrity depends on intact projections from occipital visual areas and on intact forebrain commissures. However, destruction of the pulvinar has no effect on them. The corticocortical input to this area is a converging one from V4 and area TEO. The receptive fields always include the center of gaze and most are selective for some aspect of shape or color (Gross et al. 1985). Their sensitivity to particular shapes shows constancy over variations in size, contrast, and stimulus location. Most of Gross's work to date has been performed on animals anesthetized with nitrous oxide, but others have described similar receptive field properties in awake animals. In such preparations, receptive field properties are modulated by attention, behavioral task, and certain aspects of vigilance (e.g., Richmond et al. 1983; Moran and Desimone 1985; Fuster and Jervey 1982; Gross et al. 1979).

A subset of these cells, about 5%, seems to respond selectively to faces (Bruce et al. 1981; Perret et al. 1982). In some cells, removing components of face stimuli, such as the eyes, leads to a reduction of responsiveness. Other cells require an entire intact face for any response at all to be elicited. There is another smaller subset of these cells that appears to selectively respond to images of monkey hands.

The existence of cells with specialized responses to such complex stimuli raises the question of whether these are cells which function only to recognize the presence of particular objects and whether they do so as individual elements rather than as members of an ensemble(s). Such cells were described by Konorski (1967) as "gnostic" cells and by Barlow (1972) as "cardinal" cells. Gross pointed out that similar cells for other types of stimuli have not been described, although this might be a sampling problem. Perhaps because faces are uniquely important to primates, there are specialized cells for their detection but not for other stimuli. He also pointed out that any individual neuron does not seem to possess the specificity required to recognize an individual face and would have to participate in an ensemble to achieve such recognition. There was discussion of the possibility that lesions of the area containing face cells are responsible for prosopagnosia (Meadows 1974; Tranel and Damasio 1985), but there is evidence not compatible with this suggestion in that the effective lesion site is different from the field which contains the highest density of these neurons, and the effective lesion for prosopagnosia may lead to a more generalized deficit, i.e., the inability to correctly name a particular individual member of a similar class of objects (e.g., a particular make of automobile). In the only developmental studies he has done to date, Gross has observed neurons with these characteristics in animals as young as $3\frac{1}{2}$ months old. Gross suggested that these observations on individual neurons might be related to the learning deficits observed after lesions in that shape constancy mediated by such neurons might be a prerequisite for visual learning.

Is any mechanism other than convergence required to explain the response properties of these neurons? Gross felt that convergence would be sufficient. However, it was pointed out in the discussion that the locus of this convergence might be subcortical *or* cortical. Under anesthesia, the latencies of responses in this area are about 110 ms, sufficient time for substantial analysis and reconvergence to occur (Gross et al. 1972). It was suggested that there might be interesting data to be obtained from comparing latencies on behavioral tasks utilizing face detection with the latencies observed for individual neurons. There was some disagreement about whether these cells would best be viewed as subserving perception, as subserving learning, or as serving an alerting function based on detecting *any* face. Blakemore noted that in perception an object is not only recognized, it is localized in space. Since IT cells are nonspatial, showing equivalence across retinal translation, they may be more intimately involved in categorization or learning and storage than in perception.

This discussion was concluded by noting that broad areas of ignorance remain. The mechanisms and level of the convergence that presumably underlies the response properties of these neurons is not known. The extent to which these neurons participate in ensembles and the possible characteristics of the ensembles are not understood. The extent to which these cells exhibit plasticity is not clear, and the extent to which their properties evolve during development requires further study.

Another visual area which exhibits a high degree of stimulus selectivity is area MT. This is a visuotopically organized prestriate area in which the neurons are selective for the direction and axis of motion. Lesions of MT do not affect contrast sensitivity but induce deficits in the detection of motion, smooth pursuit eye movements, and structure-from-motion perception. Only this last deficit is permanent. Zihl (1983) has described a patient whose inability to see motion has been linked to a lesion in an area possibly homologous to MT. These observations, reported by Allman, reveal another case in which the properties of individual neurons within a cortical visual area predict the consequences of lesions to that area or portions of it. This reveals that at least in some cases the functions of a particular region are accomplished by integration at the single cell level rather than being strictly dependent upon ensembles or larger aggregates of cells.

Blakemore pointed out that correlations between psychophysical tests and cellular characteristics have usually been done with the assumption that these systems are highly redundant, i.e., that other neurons in the same area have overlapping or perhaps identical response properties. He suggested that perhaps these systems are actually highly segregated and very efficient. He reported studies by Parker and Hoffman (personal communication) which indicate that individual neurons in area 17 are highly specific along more than one stimulus dimension and exhibit specificity that parallels

results from psychophysical testing. Gross noted the similarity of this observation to that made by Rolls, that degrading the characteristics of face stimuli induced equivalent rank ordering of these stimuli by human observers and monkey face cells (Rolls et al. 1985). There was substantial disagreement about whether such observations implied that very limited sets of neurons were necessary and sufficient to implement particular perceptual capabilities.

Creutzfeldt pointed out that such a model would be applicable only if individual neurons would code invariantly for one stimulus variable. This is not the case, however, and therefore the activation of any one neuron or any small set of neurons is no more than a signal that a stimulus is present, but leaves an ambiguity as to the specific type (shape, orientation, luminance, color, etc.) of that stimulus. This information can only be extracted from a comparison of activities of a large set of neurons. He discussed, as an example, the representation of colors by neuronal activities and pointed out that no individual spectrally sensitive cell can code for color and that the code for a given color can be extracted only by comparing the activity of one type of spectrally sensitive cell to that of other cells with different spectral and luminance sensitivity.

This logical necessity of comparison also applies to the coactivation of several sensory areas by certain types of stimuli. The coactivation of sets of neurons in different sensory areas and to various degrees by one stimulus may be considered as labels of qualitative specificity relative to activation patterns elicited in the respective primary sensory area. Higher order perception (cognition) therefore implies comparison of activity patterns, not only within one sensory area but also across all other sensory areas.

No simple mechanism or place in the brain can be identified as to how and where these spatially distributed activities are synthesized into a unified, unambiguous percept. Here, Creutzfeldt pointed out that it should be realized that each part of the neocortex is not only characterized by the specific pattern and origins of its thalamic, intercortical, and callosal afferents, but also by its efferents. All cortical areas including the primary sensory fields emit signals through their Vth layer cells into subcortical motor or action systems, be it the tectum, the various motor nuclei in the brainstem, the spinal cord, or the candate-putamen system. Thus, any sensory stimulus which activates a cortical region will induce a behavioral response or at least an intention to act. Activation of any sensory area thus induces a specific response (or readiness to respond), and thus represents a specific relationship between the stimulus object and the subject. Integration of these distributed activities takes place in the subcortical, efferent motor systems and will finally be represented in a unified and appropriate act (or intention to act). This emphasizes the close connection between perception and action implied in many cognitive theories.

Some questions raised by this session were: How are IT and other association cortex areas organized? What are the funcitons of its subdivisions? Can we assess its functional architecture in view of the current ignorance of its functions? Do individual neurons in many sensory areas respond to parametric variations in the same manner as the whole organism? Can effective lesion size be used to infer the amount of redundancy in a perceptual system? Can simple convergence on individual neurons account for all complex perceptions? Perhaps when some of these questions are answered, it will be possible to replace abstract, logical concepts such as "perception" and "cognition" with more *bio*logical terms.

HUMAN COGNITIVE FUNCTION: HOW DO WE ASSESS THE DYNAMICS OF UNDERLYING CORTICAL MECHANISMS?

What tools are available for the study of complex brain functions in humans and what do they (and do they not) tell us about the mechanisms of integration in human neocortex?

Gazzaniga initiated this session with a presentation of certain observations that are described in greater detail in his background paper (this volume). He addressed the questions of hemispheric specialization and hemispheric integration by evaluating the behavioral capacities of patients in whom all or portions of the corpus callosum had been sectioned and by recent evaluation of the extents of such lesions using NMR techniques. Using this approach he is reevaluating the question of right hemisphere capabilities. The use of prospective methods, in which patients are tested both before and after surgery, have proven to be important. For some previous split-brain patients, dramatic hemispheric specialization was evident. Nonetheless, most right hemispheres appear to be incapable of complex behaviors. The prospective studies reveal, however, that the post-lesion performance of the left hemisphere is reduced below preoperative levels on some tasks that are thought to call upon right hemisphere capabilities, indicating that the right hemisphere was facilitating the processing of information by the left hemisphere in the intact brain. This observation does not agree with the commonly assumed model of discrete components being responsible for the accomplishment of cognitive tasks. Rather, the idea is that particular cognitive skills reflect the activities of several subcomponents, and these subcomponents can be widely distributed in the cerebral cortex. These results also argue for a greater degree of interhemispheric integration than was previously thought to occur.

The utilization of NMR methods allows a noninvasive evaluation of the extent of the surgical disconnection of the hemispheres. In brief, these scans have demonstrated that complete surgical disconnection produces a complete

separation for perceptual and cognitive function. If the splenium remains intact, however, residual transfer of visual information between hemispheres is evident, but there is no such capacity for tactile information. In another patient, who also had a small number of splenial fibers as well as some fibers in the rostrum, there was no evidence of transfer of simple visual perceptual information. Yet, this patient was capable of matching words (one presented to each hemisphere) which both looked alike and sounded alike. In another patient, with the posterior half of the corpus callosum cut, certain somatosensory information presented to one hemisphere can be utilized to guide movements controlled by the opposite hemisphere. However, the patient exhibits this capacity in only one direction. This is possibly due to a very discrete distribution of the relevant callosal fibers such that those travelling in one direction were severed while those travelling in the other direction were not.

On the whole, these observations support a picture of these interhemispheric connections as serving highly specific, localized sensory, motor, and cognitive integrative functions.

Merzenich then presented data compatible with the idea that cortical somatosensory fields may be remodeled as a function of experience. His data indicate that receptive fields serving skin areas that are used extensively become reduced in size, and there are corresponding, smaller shifts in adjacent areas so that the receptive surface is remapped over large areas. The extent of remapping depends on which somatosensory field is examined. For example, remodelling area 1 may occur over twice the distance that is affected in area 3b. This may be due to differences between these areas in their corticocortical connections.

Remodeling can also be induced by cortical lesions. For example, if the hand area of SI is destroyed, the hand area of SII begins to display a representation of the foot surface. Systematic reorganization of the hand field in area 3b is also seen following a skin graft onto the hand, i.e., a representation of the patch that is continuous with the surrounding surface appears.

Merzenich suggested that adjacency in cortical representations (probably) results from coincident stimulation of adjacent points on the sensory surface. He also suggested that behavioral state is probably important in remodeling, in that the significance of a repetitive stimulus probably promotes the increase in the size of its cortical representation. He cited other examples from auditory conditioning paradigms where such conditioning led to increased representation of the conditioned stimulus. Such a process, especially in associative areas, may be very important for learning. He further proposed that remodeling may occur sequentially in the hierarchical components of a sensory system, and that, in many cases, there may be

progressive increases in the effects of such remodeling at higher levels of processing.

Creutzfeldt pointed out that these variations of sensory representations, as a consequence of use and training, have severe implications for what is called the neuron doctrine of perception. This doctrine states that the activation of an individual cortical neuron, or a set of these, represents the spatial localization and quality of a stimulus. If it is true that the input to one cortical point can be shifted from one region of the skin to another, excitation of that cortical point no longer invariantly represents the stimulation of the same region on the skin: before the training it may have indicated stimulation, say, of the second phalanx of the index finger and after training it codes stimulation of the finger tip. Thus, the activation of the same cortical point has changed its perceptual meaning.

The next topic discussed was the extent to which integrative mechanisms in cortex might participate directly in memory. Goldman-Rakic noted that recent studies of memory mechanisms and location have focused on the hippocampus and amygdala, while studies in cortex have focused on mechanisms of representation. She reviewed how disruption of delayed response performance results from a lesion of area 46. This is a disturbance of remembering *where* the stimulus is. This is also reflected in the inability of subjects with an area 46 lesion to direct their gaze to a remembered stimulus location in the contralateral field. Lesions of areas 11 and 12, at the temporal/frontal junction, cause a similar deficit in remembering *what* the stimulus is, leading to a deficit on matching-to-sample tasks.

These observations suggest that area 46 may be needed for the successful integration of remembered and immediately present information. This is supported by observations of single cell discharge in area 46 by Niki (1974) and Fuster (1973). These cells discharge during delay intervals in a task requiring a spatially appropriate movement to the remembered position of a target.

COORDINATE TRANSFORMATIONS: HOW ARE SPATIAL COORDINATES TRANSFORMED INTO APPROPRIATE MOTOR COMMANDS?

Our final session addressed the question of how sensory information can be integrated into appropriate behavior. This session addressed the issue of how certain sets of spatial coordinates, derived from sensory information, are translated by cortical mechanisms into appropriate commands for the initiation and execution of multijointed movements, such as the arm movements necessary to bring the fingertip to a specific point in space. This task clearly involves complex computational procedures (see Bizzi, this

volume) which permit such movements with accuracy, speed, and reliability from a variety of initial arm and body positions.

The first step in any preplanning of arm trajectory is to derive a representation based on the position of the target to be reached. This initial step is contingent upon transforming the retinal image of the target into head-centered and, ultimately, body-centered coordinates. The translation of retinotopic information into head-centered coordinates has been discussed by Andersen (this volume). In addition to the representation of the target in body-centered coordinates, the CNS must also represent the initial arm configuration in order to "plan" the arm trajectory. If the hand initial position is detected visually, then the process is identical to the one utilized for locating the target. On the other hand, if arm configuration is perceived through a combination of proprioceptors (joint, muscle, tendon receptors), then a complex and poorly understood set of transformations must occur, i.e., the position of the hand must be derived from activities specified in terms of muscle and/or joint coordinates. We do not know how the CNS accomplishes this seemingly complex readout.

Once the hand initial position and the final target are represented in the same coordinate frame then the CNS must solve the problem of representing the "trajectory," i.e., it must plan the path and the velocity of the hand in space. There is some evidence that this representation may be formed in the posterior parietal cortex and/or in medial regions of the frontal lobe. The CNS must then transform this representation in appropriate joint motion and torques.

In the past, physiologists have not specifically addressed this question. The signals from "motor" areas were assumed to activate the segmental spinal cord apparatus and somewhat mysteriously generate the desired movement. Very little attention was also paid to the fact that there are dynamic interactions between moving links that have to be handled either by the "neuronal controller" or by the biomechanical structure. These dynamic interactions will generate torques that must be integrated with those derived from the feedforward computation. Atkeson and Hollerbach (1985) have shown that these forces cannot be neglected even at fairly moderate speed.

Bizzi emphasized that even though we do not know how the CNS solves this problem, robotic work has been very useful in this area. The study of artificial systems has indicated the need to pay attention to Newtonian mechanics in the nontrivial case of a multijoint system.

In the field of robotics, two alternative approaches (termed inverse kinematics and dynamics) have been proposed to transform the planned trajectory into the appropriate joint motions and torques. One method is based upon solving the equation of motion, the other on obtaining the required torques from a lookup table indexed by the state variables $\theta,\dot{\theta},\ddot{\theta}$.

The tables may be derived either by precomputation or by associative learning. In robotics, the lookup table method was favored because computing inverse dynamics for a complex multijoint system, in a reasonable time, was quite difficult. While it makes sense to consider the dichotomy of the tabular versus analytical methods in the context of today's computers, a different perspective must be taken when considering the biological motor control system.

Recent experimental work directed at understanding coordinate transformation in biological systems has focused on muscle mechanical properties. Feldman (see Berkenblit et al. 1986) and others have suggested that a muscle is mechanically analogous to a spring, whose stiffness is a function of its activation. As with a spring, a muscle's force is a function of its length. The position at which the length-dependent forces due to opposing muscles are equal is an equilibrium position of the limb. Consequently, the CNS may maintain a desired joint position by simultaneous activation of agonist and antagonist muscles. The view of posture, in its simplest formulation, implies that each joint position is coded in the CNS by a single scalar quantity, the ratio of agonist and antagonist forces.

Studies of visually triggered head and arm movements in trained monkeys have shown that a final head and/or forearm position is indeed an equilibrium point between opposing forces. Experimental evidence indicates that the transition from one arm posture to another is achieved by adjusting the relative intensity of neural signals to each of the opposing muscles so that the equilibrium point defined by their interaction moves toward either flexion or extension of the limb. According to this view, single-joint arm trajectory is obtained through neural signals which specify a series of equilibrium positions for the limb. In this control scheme the hand tracks its equilibrium point; hence, *torque is not an explicitly computed variable.* This idea is appealing not only because of its simplicity, but also because it is fundamentally different from those used to control artificial systems such as a robotic arm.

Since in the equilibrium trajectory hypothesis, position and stiffness are the controlled variables, the problem of inverting the equation of motion (from planned trajectory to the torques) essentially disappears. According to this view, the muscles, with their mechanical and geometrical properties, seem to be capable of performing the "computation" of torques. The task of the CNS is then to transform the planned trajectory into a sequence of equilibrium positions and stiffnesses.

Andersen addressed the issue of how the retinal coordinates for an object in extrapersonal space can be transformed into body-centered coordinates. This issue and research are described in detail in his background paper (this volume). The question of how and where body-centered coordinates might be translated into motor commands was addressed in a discussion introduced

by Strick. He noted that there are four or five distinct cortical motor areas interconnected with each other and projecting to spinal cord. Each of these receives input from areas 5 and 7, and each receives unique input from subcortical motor structures. These observations indicate that each may play a unique role in transforming coordinates into appropriate motor commands.

Strick has examined wrist movements in detail in order to determine, from the characteristics of the movement itself, what information, in what form, is necessary to control movements around a complex joint (Hoffman and Strick 1986). The wrist for example has three possible planes of movement and several muscles which control the movement and positioning of the joint. The data indicate that rather than individual muscles or muscle pairs controlling movement, there are ensembles of three or four muscles involved in each type of movement. Each muscle has a "tuning curve" which describes its participation in movements of particular types from different starting positions. When a new movement is required, there are adjustments in the ensembles over the initial several trials and then a consistent strategy is adopted. Strick suggested that this is because many parameters are involved in each movement, and this complexity may also underlie the apparent requirement for the involvement of several cortical areas in the planning and execution of movements. Each area, because of its unique connections, is able to play a particular role in controlling complex joint movements.

In the subsequent discussion, there was a general consensus that there is evidence that movement direction is mapped or represented within the motor system independently of the muscles that are used to effect that movement (see, for example, Evarts 1968). But clearly, at some stage the directional commands for movement must be transformed into the appropriate patterns of muscular activity, since a variety of different limb movements may be used—depending upon initial limb position and required trajectory—to bring the hand to the same point in space. Although part of this transformation may occur within cortical motor areas, where cell discharge in relation to both movement direction and muscle force can be detected (e.g., Humphrey et al. 1970; Georgopoulos et al. 1982, 1984) it is equally clear that a transformation from required movement direction to an appropriate pattern of muscle activity can occur in the spinal cord of both invertebrate and vertebrate species (see, for example, Berkinblit et al. 1986). Thus, the eventual transformation may be computed at several stages within the nervous system and may under many normal conditions be computed by cortical-subcortical interactions.

In addition to movement direction, it is clear that motor structures must compute the appropriate forces for a given movement, since the same movement can be accomplished with varying speeds, or with differing mechanical loads opposing movement. Humphrey noted that voluntary

movements made about any particular joint must involve synergistic muscle activity at the same and adjacent joints, so that the limb is posturally supported against gravitational or other imposed forces during the movement. With the use of intracortical microstimulation methods, Humphrey and his colleagues (Humphrey and Reed 1983; Humphrey 1986) have found that single arm muscles are widely represented throughout the precentral motor cortex of the alert monkey, with a suggestion of the presence of at least three complete representations of the arm. From each of these representations, muscles acting about any of the major joints of the arm may be activated, but the observable movement is typically restricted to one or at most two adjacent joints; the muscles that are coactivated at adjacent joints produce stabilizing actions so that these joints are posturally supported during the movement. In addition to these separate representations of the arm within MI, a fourth zone was found within which microstimulation produced co-contraction of antagonist muscles at the fingers, wrist, elbow, and shoulder. Humphrey suggested that this region could represent a separate cortical zone for setting the level of joint impedance throughout the arm, independent of the speed and direction of limb movement. Data presented by Bizzi (this volume) suggests that such control exists, for stiffness fields are found to co-vary in magnitude (but not direction) at all of the major joints of the moving arm, when a subject is instructed to oppose an external perturbation of the hand during hand-arm movement. The advantages of such a separate control system for limb impedance has been discussed by Humphrey and Reed (1983), and from the standpoint of robotics by Hogan (1984). The existence of multiple representations of the arm and hand within the cerebral cortex raises the possibilities that the same muscles can be controlled by different cortical structures in different behavioral contexts (see discussion by Cynader et al., this volume), and that a number of motor parameters (speed and direction of movement, force, joint stiffness, etc.) may be "computed" by neuronal interactions within and between these various areas.

The discussion then turned briefly to the question of the role of sensory input in guidance of limb movement. The equilibrium position hypothesis elaborated by Bizzi (this volume) provides a mechanism for control of limb position and trajectory that can operate somewhat independently of continuous sensory feedback from the moving limb. However, it is probable that the importance of such feedback varies as a function of the degree of movement proficiency (familiar movements require less feedback than unfamiliar ones) and may be less important for rapid than for slow, precise movements (cf. Evarts and Fromm 1977).

The question arose as to whether there are selective motor deficits following restricted lesions in cortical motor areas, presumably reflecting the functions of restricted motor areas. It was noted that the traditional

answer is that there are indeed specific motor deficits correlated with lesions in particular locations. However, more detailed testing has caused this view to be questioned. There is some data that lesions in a specific site can induce deficits in pantomine movements despite the motor components of the movements being intact.

In closing, there seemed to be a consensus that the complexity of movement exhibited by primates could reasonably be expected to require extensive, differentiated computational mechanisms, such as those implied by the existence of multiple motor areas with multiple representations of body parts. It remains to be determined which parameters of movement are associated with particular cortical regions and what cellular mechanisms are utilized within these regions to compute appropriate commands. Finally, it is not clear whether there is a reintegration of these commands before efferent impulses are issued to the spinal cord. The "working cooperative" concept of Foerster (1931, 1936) was invoked to describe the coordinated activity of multiple motor areas in the elaboration of integrated spontaneous and purposeful movements.

EPILOGUE

The purpose of our discussions was to sketch broadly what is known about cortical integration, to highlight important areas of ignorance, and to focus on and characterize those portions of the interface between knowledge and ignorance that are both important and ripe for near-term exploitation. Within each broad problem area described above, certain crucial questions emerged which appear to be within (or nearly within) the attacking range of current techniques.

Activating systems. It is clear that these systems differ substantially from one another in terms of both anatomy and physiology, and that there are probably a few to several types of "activation." Many aspects of the physiology and anatomy of each system have been characterized. The outstanding question, which is within the scope of current methods, is "What are the target cells of these systems in cortex?" While some evidence on this issue is available for the cholinergic system in primary visual cortex, this rather straightforward question has not been systematically answered for the vast majority of transmitters, cortical regions, or species.

Selective attention. Many types of selective attention phenomena have been demonstrated, and the varied characteristics of these phenomena and their presumed substrates make it highly likely that different classes of substrates, e.g., corticocortical, cortico-subcortical, subcortical-cortical, are responsible for different phenomena, e.g., latency, duration, spatial characteristics which

have often not yet been systematically characterized at the behavioral level. Such detailed behavioral data would provide important clues about which cortical or thalamic regions might be crucially involved in particular aspects of selective attention and would guide the way for correlative, single-neuron, electrophysiological studies and for lesion studies.

Perceptions. A unifying question that repeatedly emerged during this discussion was "What is the nature of convergence and what perceptual phenomena does this process subserve?" This question initially arose while the complex receptive fields characteristic of temporal lobe visual neurons were being discussed. It is not known how information arriving from other cortical areas is anatomically and physiologically brought together onto an ensemble of neurons to generate complex, abstract receptive fields. Nor is it clear whether there are general principles of convergence or whether many different substrates are responsible for convergence in different cortical areas. The interface between "sensory convergence" and "premotor organization" was perceived as an especially crucial problem area.

Human cognition. Examples were presented in this session of how recent developments in human brain imaging have provided evidence of specific damage resulting in specific defects, when such precise anatomic/behavioral relationships were not previously evident. It became clear that the highest resolution imaging techniques available should be utilized in neuropsychological studies and that reevaluation of previously paradoxical observations may yield new insights.

Coordinate transformation. The central question in this session was how coordinates derived from sensory information are transformed into coordinates that can guide complex motor actions, such as the movement of a limb. The aspect of this question that was highlighted during the discussions was the complexity added to this question by recent observations of refined parcellation of function in cortical motor systems. This emphasizes that the sensory-to-motor coordinate transformation must be extremely complex since compatible instructions must be forwarded simultaneously to several motor areas. Furthermore, there must be substantial coordination between these motor areas because changing initial conditions, or even altering feedback in many circumstances, does not disrupt the operation of the system.

In summary, each discussion topic highlighted certain problem areas that reveal profound ignorance but offer prospects for rapid progress. It is interesting to note that there was minimal overlap between sessions, suggesting that very large areas of ignorance still intervene between these isolated regions of partial knowledge.

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