■**Special Lecture**

# Functional Organization of the Temporal Lobe and Prefrontal Areas in Human Brain : Intraoperative Investigations

George A. Ojemann*

Neurosurgical operations where the patient is awake under local anesthesia during exposure of the cerebral cortex provide a unique opportunity to investigate the neurobiology of human cognition. Notable previous investigations of this type include the observations of Foerster (1936) and Penfield (Penfield & Jasper, 1954) on organization of human rolandic cortex, and the observations of Penfield and his associates on the organization of language (Penfield & Roberts, 1959) and memory (Penfield & Perot, 1963). This paper reviews the experience of the author and his associates with investigations of the cortical organization of language and memory in this clinical setting. Those investigations have utilized several different techniques; each provides a different perspective on the neurobiology of cognition.

The most extensive experience is with the technique of electrical stimulation mapping. This was the technique used in the earlier studies of Foerster and Penfield. In that technique, a relation between an area of brain and a behavior is established when alteration of function in the brain area by the stimulating current is associated with a change in the behavior. Physiologically, application of an electric current to the cortical surface can have both excitatory and inhibitory effects, both locally and at a distance (Ranck, 1975). Empirically, stimulation of primary motor and sensory corticies usually evokes positive responses, movements or sensory events. However, stimulation of association cortex, at least at currents below those associated with afterdischarge, usually has no positive effects. However, at some association cortex sites application of the current will disrupt an ongoing behavior, such as a measure of language or memory. Presumably at those sites, the predominant effect of the current is to block neuronal function by depolarization. In terms of neuronal activity, the current has apparently produced a temporary lesion. When a behavior fails with that stimulation induced temporary lesion, function at that site must be ESSENTIAL for that behavior. The investigations of classical behavioral neurology establish relations between brain areas and function in the same way, identifying the location of lesions that are associated with failure in a behavior. Thus, both stimulation mapping and structural lesion investigations identify brain areas essential for a behavior. Advantages of stimulation mapping include the ability to alter function in relatively small areas

*Department of Neurosurgery, University of Washington, Seattle, WA, USA

of cortex, with appropriate attention to stimulation current levels, the ability to map wide areas in an individual subject, and the ability to utilize the reversible nature of the lesion to probe specific functional roles for a brain area, such as the relative roles in language compared to recent verbal memory.

Although stimulation mapping identifies the location of essential areas for a behavior, it provides limited information on the physiologic mechanisms active there during the behavior. We have utilized a second technique to obtain some insight into this issue. In these studies, the electrocorticogram (ECoG) was recorded from the cortical surface at sites previously identified by stimulation mapping as essential for a behavior. These recordings were made during that behavior, with activity compared to that recorded from nearby cortical sites not essential for that behavior, and at the essential sites, to that recorded during a control behavioral.

The other techniques utilized during our intraoperative studies identify where neurons are active and thus PARTICIPATE in a behavior, but do not necessarily establish that the activity is essential for the behavior. Thus, these techniques provide information similar to that derived from Positron Emission Tomographic (PET) or functional magnetic resonance (fMR) imaging studies that identify where neurons are active during a behavior by the associated changes in blood flow and oxygen utilization. The techniques we have used in the operating room to obtain this type of information include optical imaging of the "intrinsic signal" the subtle change in surface reflectance that occurs when neurons are active, and extracellular microelectrode recording of activity of individual neurons.

## ESSENTIAL AREAS FOR LANGUAGE AND RECENT VERBAL MEMORY

The major findings from our electrical stimulation mapping studies during measures of various aspects of language and recent verbal memory can be summarized as follows. In an individual subject, sites in perisylvian dominant hemisphere cortex essential for some one language function, such as object naming, are often localized to several separate areas, each 1-2 square cms in extent (Ojemann, 1983; Ojemann et al, 1989). These sites often, but not always have sharp boundaries separating them from surrounding cortex not essential for this behavior (Ojemann, 1983; Ojemann et al, 1989; Whitaker & Ojemann, 1978). There is usually one posterior inferior frontal site and one or more temporoparietal sites.

However, when the location of these sites is compared across subjects, substantial variability is found in their exact location (Ojemann & Whitaker, 1978a; Ojemann et al 1989). A few subjects seem to have essential sites only frontally, or only temproparietally (Ojemann et al, 1989). In a series of 117 left dominant subjects evaluated with stimulation mapping during object naming (Ojemann et al, 1989), 79% had an essential site in posterior inferior frontal cortex, immediately in front of face motor cortex. But elsewhere in the perisylvian area, including all of Wernicke's area, no more than about one-third had essential sites in any one region. Only two-thirds of these subjects had an essential language site anywhere in superior temporal gyrus.

This variability was correlated with several patient characteristics, including gender and preoperative verbal ability

(Ojemann et al, 1989). Women were more likely to have only frontal language sites, and had fewer sites in the parietal operculum than men, findings similar to the gender differences in the effect of brain lesions on language reported by Kimura (1983), who suggested that women were somewhat less dependent on posterior language areas than men. In our intraoperative studies, we also identified differences in localization of sites essential for naming related to preoperative verbal ability, as measured by the preoperative verbal IQ (VIQ). Patients with high preoperative VIQs had sites essential for naming in middle temporal gyrus, those with lower VIQs in superior temporal gyrus. Sites also covered a somewhat larger area in those with lower VIQs. On the other hand, we identified no differences related to subjects age, or time of onset of the condition leading to the craniotomy. Using the extraoperative stimulation mapping technique through chronic subdural electrode arrays, we have mapped language in children as young as 4 years old (Ojemann et al, 1989). Even in these young children, sites essential for naming are highly localized.

When sites essential for several language functions are identified in an individual subject, the general finding is separation. It appears that in cortex, different aspects of language depend on separate systems. This has been most dramatically shown for naming of the same objects in two different languages, whether two oral languages (Ojemann & Whitaker, 1978b; Ojemann, 1983, 1994; Rapport et al, 1983; Black & Ronner, 1987), or an oral and sign language (Mateer et al, 1982; Haglund et al, 1993a). In each situation, some degree of separation of sites essential for the different languages has been identified in most subjects. Separation of essential sites has also been established for naming compared to reading (Ojemann, 1983, 1989), object naming compared to recent verbal memory for an explicit object name (Ojemarm, 1978, 1983; Ojemann & Mateer, 1979; Ojemann & Dodrill, 1985, 1987), and recently, for several semantic tasks including separation of sites for naming and word reading from those for generation of verbs from nouns, and of sites for naming one semantic category from those essential for naming another category (J. Ojemann et al, 1993 and forthcoming). Separation of sites for different aspects of language is evident in both frontal and temporal-parietal parts of perisylvian cortex. For recent verbal memory, stimulation mapping suggests different roles for the frontal or temporal-parietal cortical sites, with the former related to memory retrieval, the latter memory acquisition and storage (Ojemann, 1978,1983; Ojemann & Dodrill, 1985,1987). These studies, along with evidence from the effects of temporal lobe resections, and microelectrode recordings during memory measures establish a role for lateral cortical, as well as medial hippocampal temporal lobe in recent memory.

It is in this context of separation of sites essential for different aspects of language that the presence of sites essential for several aspects is of particular interest. One set of such sites is in posterior inferior frontal lobe immediately in front of face motor cortex, where all output from language is altered by stimulation, regardless of the task generating the output. These sites represent a final motor pathway for all language output. These sites are also essential for the bilateral orofacial movements required for single speech gestures (Ojemann & Mateer, 1979; Ojemann, 1983).

More widely in inferior frontal and superior temporal gyri are sites essential for the generation of sequences of speech gestures (and language output). Thus, the areas essential for motor aspects of speech extend beyond Broca's area, to include superior temporal gyrus and anterior inferior parietal operculum. For brain lesions to be associated with a permanent motor aphasia, this entire area must be destroyed, rather than just Broca's area (Mohr, 1976). Most of these same cortical areas also are essential for the decoding of speech sounds (Ojemann & Mateer, 1979; Ojemann, 1983). This overlap of sites essential for motor aspects of speech and decoding of speech sounds is the pattern predicted by the "Motor Theory of Speech Perception" (Liberman et al, 1967), a theory derived from psycholinguistic studies that proposes that because of the categorical nature of speech sound decoding, that process involves creation of a motor model. Alternatively, both processes may depend on a common function such as precise timing (Tallal, 1983; Calvin, 1983), with the areas of cortex where both are altered essential for that.

A number of other consistent relationships have been identified between sites essential for different aspects of language. Sites essential for object naming, and those essential for retaining that name in explicit recent verbal memory are usually separate (Ojemann, 1978,1983; Ojemann & Dodrill, 1985). Sites essential for semantic processes such as verb generation usually are adjacent to those for more basic aspects of language such as naming or word reading.

ECoG recordings from sites essential for one aspect of language, object naming, have identified several changes that are significantly more evident at those sites during the language task compared to a control spatial task using physically identical items, and during the language task, significantly more evident at the sites independently established as essential for that task by stimulation mapping than in surrounding cortex (Fried et al, 1981; Ojemann et al, 1989b). Those changes are slow potentials at frontal sites, and local desynchronization at temporoparietal sites. A recent study has identified similar ECoG changes at temporoparietal sites during language measures (Crone et al, 1994). The frontal and temporoparietal changes we identified occur simultaneously, appearing shortly after presentation of the item to be named. This is evidence for parallel processing between frontal and temporo-parietal areas essential for language. Parallel processing at sites important for a function distributed across cortex has been a feature of the physiologic mechanisms for a number of functions in primate investigations (Goldman-Rakic, 1988). Although our studies delayed overt language output to a later cue, the frontal slow wave that appears in our silent tasks is similar to the premotor potential that occurs with the overt output, suggesting that silent language processing progresses to the stage of motor effector readiness. The temporoparietal desynchronization is an effect that can be produced in experimental animals by activation of the thalamocortical activating system (Jasper, 1960), suggesting that this system is important in selecting the cortical areas essential for a particular aspect of language.

## AREAS PARTICIPATING IN LANGUAGE AND RECENT VERBAL MEMORY

Intraoperative investigations of areas

participating in language and recent verbal memory utilized optical imaging of the "intrinsic signal" surface reflectance changes, and extracellular microelectrode recording of single neuronal activity. The intrinsic signal represents a subtle change in tissue volume that occurs where neurons are active (Haglund & Blasdel, 1992). It was initially described in studies of primate visual cortex, and ascribed to blood volume changes, but more recent studies have identified intrinsic signals in tissue slices which have no blood supply, so at least part of the effect depends on something else, probably neuronal and glial swelling from the ionic shifts associated with activity. We have used this technique during object naming and recent verbal memory measures, and compared the findings to stimulation mapping localization of areas essential for the same functions in the same subjects (Haglund et al, 1992, 1993b). The optical imaging changes were present in the same general areas as the stimulation mapping changes, but the optical changes covered a somewhat wider area, suggesting that the area where neurons participate in a function extend beyond those essential for it. The optical imaging studies demonstrated separation of area active with naming from those active when an explicit name must be retained in recent verbal memory, as was seen with stimulation mapping.

Microelectrode recording of changes in neuronal activity during various aspects of language has greatly extended the apparent extent of the area where neurons participate in language. Because microelectrode recording is invasive, in our studies it has been restricted to areas that will be subsequently resected, which excludes recordings from areas identified as essential for language by stimulation mapping. Nevertheless, recordings obtained during naming identified neurons changing activity throughout lateral temporal neocortex of both hemispheres, in area clearly not essential based on stimulation mapping findings, effects of intracarotid amobarbital perfusion, and effects of subsequent surgical resection (G. Ojemann et al, 1988; J. Ojemann et al, 1992; Schwartz et al, 1992 and forthcoming). The proportion of sampled neurons changing activity with naming or word reading is about the same in either hemisphere. Lateralized differences were identifted for naming but not word reading, with significantly more evidence for inhibition of activity during both overt and silent naming in both superior and middle temporal gyri in the left, dominant hemisphere, and significantly more excitation, but only with overt naming and only in middle temporal gyrus in right, nondominant hemisphere (Schwartz et al, 1992 and forthcoming). Based on these findings, it appears that participating neurons for a language function are widely distributed throughout much of neocortex.

When recordings are made from the same neuron during several different aspects of language, the most common finding is that a neuron is excited or inhibited by only one of the measured functions. This includes neurons excited (or inhibited) by naming in only one of two languages (Ojemann, 1994), with naming in only the oral language and not sign language (Haglund et al, 1993 a), with either naming and word reading but rarely both (Ojemann, 1989; Schwartz et al, 1992 and forthcoming), with naming or recent memory for an explicit name but not both (Ojemann, 1994b), and with auditory perception of a word, but not its overt repetition (Cruetzfeldt et al, 1989a,b; Ojemann, 1991). Thus, the separation of various aspects of language present with stimulation mapping identification of essential areas extends to the widely dispersed participatory neurons. Each aspect of language is represented by a system that includes highly localized essential areas in the dominant hemisphere, and widely dispersed neurons in cortex of both hemispheres, with the system for one aspect of language such as naming separate from that for another aspect such as reading (Ojemann, 1991b). All aspects of a system seem to be activated in parallel at the initiation of the specific language behavior.

Recordings during recent memory for explicit object names identify changes in activity in a large proportion of neurons in dominant lateral temporal cortex, in one study 75% of the sample and in another 67% (G. Ojemann et al, 1988; Haglund et al, 1994). Most of the changes in activity are during acquisition or retrieval, and not during the period when the memory is stored. The presence of these changes is further evidence for a role of lateral temporal neocortex in recent memory. Although these changes are present in a very large number of neurons, they are also very transient, becoming less evident on a second retrieval of the same item from memory, although reappearing when a new item enters, or is initially retrieved from memory (Haglund et al, 1994). Thus, this activity most likely has a role in promoting mechanisms of retention located elsewhere.

Our recent study of changes in temporal neocortical activity with paired associate learning has further delineated the roles of these different systems of neurons for different aspects of language and memory (Weber & Ojemann, 1995). In that study, neurons were divided into those related to overt word reading, those related to recent memory for an explicit word, and those not related to either function. Changes related to learning of an association between word pairs were identified in those neurons related to overt word reading, and those related to neither overt reading or memory. Neurons related to recent word memory did not have specific changes related to learning of an association between words. Thus, learning and memory seem to be disassociated at a neuronal level. Neurons related to overt word reading had high levels of activity during paired associate learning in those subjects who learned rapidly. This level of activity was greater than that present during word reading alone. The activity declined once an association had been learned. This same class of neurons had low levels of activity in subjects who learned few associations, a level of activity below that present with overt word reading. Neurons unrelated to overt reading or memory had the opposite pattern, very inactive in subjects learning associations readily, and very active in those learning associations poorly. From this study it appears that learning of an association involves those widely dispersed neurons that are part of the overt, motor system for that function. PET evidence that learning might involve increased activity in motor areas for language has been presented by Raichle (1990).

Extracellular microelectrodes often record activity from several nearby neurons. That activity can be separated based on the amplitude and morphology of the action potentials from the nearby neurons. When the relation of nearby neurons to an aspect of language is examined, the most common finding is that the neurons change activity with different behaviors (J. Ojemann et al, 1992; Schwartz et al, 1992 and forthcoming; Weber & Ojemann, 1995). This is a somewhat unexpected finding as neocortex is usually considered to be organized in columns of similar function. Perhaps human association cortex is organized in columns with repetitions of a repertory of functions each subserved by different neurons, whose proximity aids in the development of associations.

## CONCLUSIONS

These observations on the organization of neocortex are but one aspect of the basic neurobiology of human cognition that may require revision based on the findings from our intraoperative investigations. Those studies provide considerable evidence for a model of the cortical organization of language and memory that includes separate systems for different aspects of language and for recent verbal memory, systems that include both localized essential areas and widely distributed neurons. Those studies have also indicated the substantial variability between subjects in the cortical organization of language, and some relations of that variability to gender and verbal ability. A role for temporal neocortex in recent verbal memory has been established by these intraoperative investigations. However, they have also demonstrated the importance of the systems related to overt aspects of language rather than this memory system in the learning of associations between words. More findings from these studies that suggest revisions in the traditional models for the neurobiology of language and memory will likely be forthcoming. For example, our microelectrode studies have focused on changes in frequency of activity, but there is some evidence of unusual temporal patterns independent of changes in frequency that are related to language (Cruetzfeldt et al, 1989a,b) and recent verbal memory (Ojemann et al, 1990). These and other lines of intraoperative investigations of the neurobiology of human cognition are likely to provide additional new insights into their cortical mechanisms.

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