Interview

Interview with George A. Ojemann

■ George A. Ojemann was born in Iowa City, and received undergraduate and medical degrees from the University of Iowa, and his neurosurgical training at the University of Washington in Seattle. He has been on the faculty of that school ever since, except for a brief period at the National Institutes of Health in Bethesda, MD. He is presently Professor of Neurological Surgery. His clinical interest is in the surgical treatment of epilepsy. In addition to the research interests that are the subject of this interview, he is past chairman of the neurosurgical certifying board, a present member of the neurosurgical training program accrediting body, a member of the NIH Neurological Institute Advisory Council, and the President-Elect of the American Academy of Neurological Surgery. He is also a recipient of an NIH Javitts Award, a Distinguished Alumni citation from the University of Iowa, and an honorary Doctor of Sciences degree from the Medical College of Ohio. His wife is a neurologist with interests in epilepsy, and his two sons are in neurosurgical training programs, while his daughter is in medical school. ■

JOCN: You have approached the study of human cognition from the operating theater. This represents a truly unique vantage point. How did you get into this approach?

GAO: My interest in the relation between the brain and behavior was probably derived partly from my father, Ralph Ojemann, who was Professor of Developmental Psychology at the University of Iowa for most of his career. I don't really know where the interest in medicine came from—there was only one rather distantly related, but much admired physician in our family prior to my generation—but that interest goes back to my early childhood. The family influence may be stronger than I realize, as my older brother also went into medicine and became a neurosurgeon, now at the Massachusetts General Hospital. When I was in medical school I found neurology particularly fascinating, in part reflecting contact with some great teachers: Adolph Sahs at Iowa and Raymond Adams and Miller Fisher at Harvard, and in part reflecting the diagnostic challenges neurology presented in the pre-CT era.

I came to Seattle intending to be a neurologist, but there encountered Arthur Ward, Jr., the head of neurosurgery at the University of Washington. Art had begun his career in neurophysiology at Yale, in the era of John Fulton. He was persuaded by Percival Bailey to become a neurosurgeon so he could use the clinical opportunities those operations present to make neurophysiologic observations in humans. Art eventually trained in neurosurgery at the Montreal Neurological Institute with Wilder Penfield. So he brought both the Yale neurophysiological tradition, and the MNI tradition of awake epilepsy surgery as a vehicle for studying neurophysiology in humans, to the University of Washington program. Those were the traditions I encountered, and formed the basis for my career.

While training with Art, I became interested in the relation of thalamus to language. We occasionally saw anomia after dominant thalamotomies, which was not well explained by the theories of the neurobiology of language then formulated. In those days, thalamotomy for dyskinesias was a frequently performed operation, with the patient awake so that physiologic guides could be used to place the lesion correctly.

When I finished my neurosurgical residency I became a Clinical Associate in the Surgical Neurology Branch at NIH. There with a psychologist, Paul Fedio, and the support of the neurosurgeon John Van Buren, I adapted Penfield's technique of electrical stimulation mapping to the thalamic electrodes, and we mapped out language representation there. Later we extended the stimulation mapping technique to recent verbal memory measures and established some of the recent memory representations in lateral thalamus. When I first returned to Seattle to join the neurosurgical faculty at the University of Washington, I continued those studies, and extended them to mapping the location of sites where cortical electrical stimulation, during awake surgery for epilepsy, disrupted a variety of measures of different language and recent-memory-related functions.

Art Ward's major interest was in neuronal electrophysiology, particularly activity of single neurons in epilepsy. He had developed techniques for extracellular microelectrode recording of neuronal activity in humans during those awake epilepsy operations. I assisted him in

some of these studies of activity of human "epileptic" neurons. Based on that experience I thought we could make similar recordings during measures of language and memory, preferably in neurons that did not have the bursting activity that characterizes "epileptic" neurons.

The opportunity to do that developed in the mid-1980s, when Otto Creutzfeldt, a neurophysiologist from Germany, expressed an interest in attempting this and arranged a sabbatical year with me. At the time we didn't know if there would be any activity that we could record related to language or memory. Subsequent experience has shown that there are many neurons, widely distributed in both hemispheres with significant changes in activity to these measures, even though we restricted our recordings to brain areas that were not crucial for those functions, areas that we planned to remove as part of the surgical treatment of the epilepsy. With the recognition of the efficacy of surgery for epilepsy, the number of operations increased. This allowed an increase in the opportunities to make observations on the neurobiology of cognition, as well as undertake a therapy that helps a significant number of patients. That's the wonderful thing about this career: there is both a chance to really help someone, and to make new observations on what I find a fascinating subject—the brain mechanisms that underlie behavior.

JOCN: This approach is so unique and is such a limited resource that it would be interesting to know some of the mechanical details of the process. So before getting into your many observations, could you capture for us the subjective experience of the patient? They are awake, their skull is open and you are recording neural activity to discrete stimuli. Does it seem strange or psychologically uncomfortable to them?

GAO: I've had to think a bit as to how to respond to this question. Remember that the patients are awake primarily for clinical reasons: to obtain electrocorticographic recordings without the effects of anesthetic agents, and to allow for functional mapping. Thus the patients are highly motivated to cooperate during the period when they are awake. There are quite a number of things that they, and the surgeon, must do during the time they are awake. I don't think either the patient or I are very introspective during that time. You are right that there is a bit of tension, but it's of the sort associated with "getting the job done." When the patient's role is active, as during functional mapping or the microelectrode recordings, they generally report being less uncomfortable than when their role is passive, where they notice things related to being unable to move around as much as they would like. Patients generally do not experience discomfort, or much of any other sensation from the head, since the surface of the brain really doesn't have any pain or touch detectors. Those in the scalp and dura have been blocked by local anesthesia placed before they were awakened.

Having the patient awake during the operation does require some preoperative preparation. I try to be sure they know what will happen, and what will be expected of them. In that preoperative education we use several videotapes that have been made of these procedures, and sometimes have the patient talk to someone who has already undergone the operation. During the operation, it is important to be continuously in contact with the patient during the time that they are awake so they know what's coming next. It is especially important when they first awaken from the Propofol intravenous anesthesia we use so that they are asleep while the field block of local anesthesia, and the craniotomy are done. Surprises are to be avoided.

JOCN: OK, so you are now looking for cellular responses to cortical neurons during a cognitive task. In primate research there is a tremendous training period involved in preparing the animals for the task. This is followed by a huge amount of data collection on these well-trained animals. How do you view your moment in the brain of one individual? In short, how do you frame the question you want answered under the far more taxing conditions of the human surgical theater?

GAO: First, there are considerable practical restrictions on what can be done. There is a substantial time restriction. We try to limit any intraoperative research studies to about 30–45 minutes. Any tasks must be simple enough that they can be reliably done in the OR, and can physically be done in the patient's position lying on their side. Second, in part because of this unusual environment, we design the tasks so that we can be reasonably sure that they were done. We try to avoid the "silent" tasks currently popular with fMRI protocols, where one can only assume that they were done. We try to embed control measures in the tasks, since performance outside the OR may not reliably indicate performance in the OR. That usually means that individual task stimuli must be simple and brief: an object picture, a word or short sentence, no paragraphs. This has been important in all our intraoperative studies, regardless of the physiologic measure: electrical stimulation, imaging of the "intrinsic signal," electrocorticographic correlates or microelectrode recording of neuronal activity.

The general strategy has been to compare one behaviorally defined state to another that apparently differs by one cognitive process. A favorite one has been to compare activity during verbal identification of objects or words, to that when the same object or words must be retained in explicit recent verbal memory.

The location of our investigations is dictated by the clinical situation, so we select the cognitive area to study based on what is known about functions of the area

which will be accessible to us. Since many of the surgical opportunities involve the temporal lobe, many of our studies relate to recent memory and learning. Because of the unique nature of this opportunity, we have been concentrating on cognitive processes that are uniquely human. Thus most studies examine verbal processes, and only a few of our studies have utilized visuospatial materials that would also be suitable for nonhuman primate investigations. I've been criticized some for that decision, since it makes comparison between human and nonhuman primate findings more difficult. It has also been suggested that we should concentrate on "simpler" processes such as primary visual or auditory perception, rather than more complex processes like language. My own view is that if the process is represented in nonhuman primates, it can probably be better studied there, with human studies reserved for cognitive processes, such as language, that are poorly or not at all represented in nonhuman primates.

With the evidence we've accumulated of substantial variability between subjects in some of our findings, we try to acquire as much data as possible in an individual subject. Because of the time restraints, we collect as much data simultaneously as possible. For example, we continuously try to increase the number of neurons we can simultaneously record from multiple sites in the brain areas available to us. That area is determined by clinical considerations, since the invasive nature of microelectrode recording restricts it to brain areas that will be subsequently resected as part of the surgical treatment of the underlying disease that led to the operation. You are right, however, about one major advantage we have over nonhuman primate studies: our subjects are much easier to train.

JOCN: Concentrating on uniquely human capacities makes sense. What do your studies tell us about lateralization and localization? You mentioned variability. Is the variance seen within the hemispheres or between the hemispheres? Also, would you care to comment on some recent fMRI data that suggest that language processes are frequently bilaterally represented? Do you think it is true, or could those activation patterns represent co-activation due to the homologous callosal input in the right hemisphere?

GAO: Intraoperative investigations are not ideal to address issues of lateralization, as one does not have the opportunity to sample activity in both hemispheres at the same time, and rarely in the same subject. We use intracarotid amobarbital perfusion assessment of language and memory functions for lateralization information in individual patients. However, one can obtain population lateralization information from intraoperative studies. Those findings depend on the technique used in the intraoperative studies. The intraoperative electrical stimulation mapping technique relates an area of brain to a behavior when that behavior fails while the local brain area is inactivated (probably by depolarization blockade). Thus stimulation mapping indicates areas of brain that must be functioning at that point in time to execute the measured behavior. I've called these "essential" areas. Effects of brain lesions on a behavior and intracarotid amobarbital perfusion are other methods for identifying "essential" areas, and make the link with a behavior in an analogous manner.

On the other hand, microelectrode recording and optical imaging of the intrinsic signal indicate where neurons are working, but not necessarily that they are "essential" for the behavior. PET and fMRI show where neurons are presumably working (insofar as that work is reflected in blood flow and oxygen extraction changes), but not whether they are "essential" for a behavior. This is an important consideration in interpreting PET or fMRI findings that is often overlooked. I call the areas of brain with changes in neuronal activity "participating" areas.

Language lateralization findings in our intraoperative studies are different, depending on whether the technique identifies "essential" areas, or "participating" areas. "Essential" areas, based on electrical stimulation mapping, seem to be strongly lateralized to the hemisphere considered dominant on the pre-operative Wada test. This includes naming in sign and multiple languages, reading, and recent verbal memory measures.

However, when one looks at the microelectrode recordings during language tasks such as naming or word reading, the proportion of neurons changing activity in temporal lobe is the same in *both* hemispheres. Neuronal activity during language appears to be widely distributed, even in the "nondominant" hemisphere. We were able to identify some significant differences between the hemispheres for object naming, though not for reading. During object naming, left "dominant" hemisphere neuronal activity was predominantly inhibition, a reduction in activity compared to the control condition. This was present during both overt and silent naming. Since these recordings are from non-essential portions of left temporal lobe, perhaps this inhibition reflects an inhibitory surround, sharpening an excitatory area, whose location we can only infer might be "essential" areas. Microelectrode recording is too invasive to be done in brain that will not be resected such as "essential" areas for language. Right temporal cortical neuronal activity during naming was predominantly excitatory, during overt naming only. We have some currently unpublished data that the changes observed in the left hemisphere before overt language tasks precede those on the right. So "dominance" may be a matter of timing, or excitation versus inhibition, but not the presence or absence of neuronal activity during a language behavior.

Intraoperative stimulation mapping is a great tech-

nique for addressing issues of intrahemispheric localization of "essential" areas. For a particular language behavior such as naming, "essential" areas are very focally localized in an individual subject. These are usually localized to multiple sites each of which has a surface area of about 1–2 cm2. However, there is marked variability in the exact location of these sites between subjects, with different patterns of localization related to preoperative verbal performance, as measure by the VIQ, and subject gender. Different language behaviors often have separate "essential" sites, including different sites for the same linguistic function in different languages. There is much more to the intrahemispheric localization findings derived from intraoperative studies, which perhaps should wait for the next question.

JOCN: Indeed, and fascinating. So let's consider the organization of language in the left hemisphere. In general terms language can be broken down into lexical processes and grammatical processes. You have concentrated on the former. First, the variability question: How great is it? And, have any of the patients come to autopsy allowing for a histological analysis of the different areas from one patient to another? Might there be a common underlying anatomy?

GAO: Although we have the most data on lexical processes, we have some information on intrahemispheric localization of syntactic processes as well, identifying essential areas for grammatical processes with the electrical stimulation mapping technique. I'll come back to that later, perhaps. To address the issue of variability in location of essential areas for a semantic task, object naming, we pooled the maps from over a hundred patients, all left brain dominant for language based on the preoperative Wada tests. We aligned these maps by the central sulcus and sylvian fissure and then divided them into arbitrary zones each about 1.5–2 cm wide on a single gyrus. The zone immediately in front of face motor cortex contained sites essential for naming in almost 80% of the sample. No other zone contained essential sites for naming in more than about 36%, including all the zones that would cover Wernicke's area. There were a few patients in whom we could not find any frontal "essential" sites for naming, and a slightly larger number in whom there were no identifiable temporoparietal naming sites. This variance is even greater than the considerable anatomic variance described for the cortical pattern at the end of the sylvian fissure in human brains. And the one study of cytoarchitectonic variance (in 4 brains for one area TP) though showing substantial variability, did not have anything close to the variance we found in functional localization. We have subsequently published similar studies for localization of sites essential for sentence reading, in 55 patients, and for changes in performance on a recent verbal memory measure, in 'around 20 patients. All show substantial variability in localization between patients. There seems to be functional significance to some of the localization patterns.

One of the most robust effects we have seen is generally larger "essential" areas for naming in those with low compared to high preoperative VIQs (smaller is better). Another is in the combination of location of sites essential for naming and those for sentence reading (in the same subject). Patients with highest preoperative VIQs had essential sites for naming in middle temporal gyrus, and for reading in superior gyrus, while those with the lowest VIQs had the reverse pattern. We have also found gender differences in these patterns, with women less likely to have essential sites in parietal operculum (supramarginal gyrus), and more likely to be in the group with only frontal essential sites. These findings support the view derived from stroke patients, that some women are less dependent on temporoparietal cortex for language. Interestingly, we found no localization differences related to age. We have data on localization of naming from age 4 to age 80. Of course, all the naming measures are relatively overlearned, even in the 4-year-olds.

Fortunately, patients rarely die after epilepsy surgery. We have reported histologic findings in one patient who died two years after he had stimulation mapping of naming. That study was directed at the pattern of neuronal branching in language or non-language areas. Using Golgi stains we found some differences between the two areas (as identified with stimulation mapping) in ratio of basilar to apical dendrites.

JOCN: What do you make of the startling fact that less cortex is used for high verbal IQ patients?

GAO: As to this issue of "less is more," that smaller areas of cortex seem to be essential for a language function in those with more facile language, I suspect that this is a general principle of cortical function: Many widely distributed neurons are active with a new novel item, especially if it represents explicit information to be remembered and even more if it is to be learned. In our recordings during recent explicit memory tasks, the activity in temporal cortical neurons occurring at initial retrieval of an item entered into recent memory diminishes with each subsequent retrieval of that item after additional distractions. In our recordings during a word pair associates learning task, once an association was learned, activity began to decline within one or two trials. The neurons that we identified having greater activity for those word pairs whose associations are learned are then characterized by inhibition of activity when the task is to just identify the same words but not learn an association between them. Our hypothesis then is that when new information is introduced into memory, or new associations learned, many widely distributed neurons are active, but as this information is used repeatedly, the pool of neurons active during use of that item becomes progressively smaller, with inhibition of many

of the neurons originally active. Whether this “frees up” neural networks for other uses we do not know. Maybe it is just an energy matter, reserving widespread excitation with its energy demands for only the times when it’s needed. Since we do not know what feature it is that makes a site “essential,” one could only speculate why these sites also become smaller in those with facile language, but it may indicate that this “focusing” of activity with repeated use is more effective in those subjects.

In addition to these findings, our microelectrode studies suggest several other principles of the organization of the neural networks in human association cortex that subserve various cognitive processes. An individual neuron generally changes activity in one direction for only one behavior, within the limits of the range of behaviors sampled. A neuron that is active with naming is rarely active in the same direction with reading. A neuron that is excited when identifying an object by name is likely to show no change or be inhibited when this same object name is to be retained in explicit verbal memory, even though the behavior evident during identification or memory encoding is identical, overt production of the object name. What we have not seen are “general purpose” neurons changing activity in the same way with all verbal tasks, or all verbal memory tasks. From these observations we conclude that the neural networks for different behaviors are generally separate.

Another general principle is based on findings from simultaneous recordings from nearby neurons, so close together that activity is picked up by a single microelectrode. These neurons usually change activity to different behavioral measures, suggesting that at any one place in human association cortex, the separate networks for different behaviors are interlaced, rather than having each network segregated into separate columns or modules.

JOCN: Why have you used object naming so extensively?

GAO: There are now three reasons. One is historical. My stimulation mapping studies were a direct extension of Penfield and Robert’s work, and they used naming. The second is that naming is about the only language behavior that fails in all brain lesions associated with language deficits. The third is that we have done two studies to determine whether sites essential for naming were useful in planning cortical resections to minimize the risk of a postoperative aphasia. In both we found that when a resection had come close to a site essential for naming, patients were likely to show postoperative language disturbances. The postoperative language disturbances were unrelated to size of the total resection, preoperative verbal ability, or degree of seizure control. “Close,” in one study, was defined as 20 mm along a contiguous gyrus; that study used changes on the Wepman aphasia battery as a measure. The other study defined “close” as 7mm, but the measure was a clinically evident aphasia. So the sites on the surface of cortex where stimulation disrupts naming predict the effects of tissue removal that includes not only the surface but also buried cortex up to that level. This suggests two interesting things: “essential” language sites are preferentially localized to the crowns of gyri and are hardly ever only in buried cortex, and that the connections from those sites go straight down into the white matter, otherwise those connections would be damaged by the resection.

Moreover, when one gets close to sites “essential” for naming, the deficit is in multiple aspects of language. We also know that “essential” sites for naming, while a good screening measure for oral language localization, do not tell the whole story. In fact, there is good evidence for separate “essential” sites for many aspects of language, including those areas essential for syntax that are separate from sites essential for lexical tasks. Perhaps we can discuss this further.

JOCN: What are the “essential” sites for syntax? Does it tend it tend to be more localized than the lexicon?

GAO: Stimulation mapping investigations indicate that different aspects of language have separate “essential” sites in perisylvian cortex. For example we find separate sites for naming versus reading, for different semantic categories (animals versus tools), and apparently for syntax. We have identified sites where the change in syntax with stimulation is in both posterior frontal lobe (generally superior to sites related to all speech output), and posterior temporal lobe. Those sites were identified on sentence reading tasks. At most sites related to reading, the effect of stimulation is to greatly slow reading of all words. However at these sites reading remains fluent but errors are made on verb endings, pronouns, and conjunctions—effects we interpreted as related to syntax. These errors are pretty remarkable, as sentence reading is a rather easy task, usually done quite reliably. The total area from which we have evoked these effects is about the same size as the total area from which errors specific to semantics have been evoked. There are also separate “essential” sites for explicit verbal memory compared to generalized semantic memory. Thus both the widespread neural networks and “essential” sites for different aspects of language, and language compared to explicit verbal memory, are separate.

It is in this context of general separation of “essential” sites for different aspects of language that the regular occurance of changes in measures of two different functions with stimulation of the same site becomes significant. We found the ability to mimic orofacial speech gestures and to decode speech sounds were both often altered from stimulation of the same posterior inferior frontal, superior temporal, and anterior parietal sites. We suggested that the common feature altered by stimulation of this cortex might be a motor mechanism important to speech decoding, as suggested by the motor

theory of speech perception, or a timing mechanism common to both language production and perception.

To complicate matters, we have recently been investigating differential effects of stimulation on object identification compared to action identification in response to the same cues that contain both objects and actions. There are certainly differential effects in temporal cortex, with action identification more readily disturbed.

We have not yet specifically investigated syntax during microelectrode recordings. One would expect separate networks widely distributed even in nonessential areas (and hemispheres) based on the findings with other aspects of language during those neuronal recordings.

JOCN: One final question, where do you see future opportunities for this kind of work?

GAO: Perhaps the most important immediate issue, from my view, is to establish relationships between electroclinical findings, and those from PET and especially fMRI. We really don't know much about the relation between the metabolic surrogate measured by PET and fMRI and what neurons do. We know somewhat more about what the electroclinical findings represent. For example, sites producing repeated errors with electrical stimulation are apparently crucial for that function, based on the effects of resecting near to that site. Are the sites with fMRI changes also crucial? Or do they represent metabolic changes from the neural activity we record with microelectrodes that seems to be very widely distributed? What are the PET-fMRI correlates of the relative inhibition we record with microelectrodes? Our preliminary findings comparing fMRI to electrical stimulation mapping during similar (but not identical) language measures in an individual subject have not shown very close correspondance in temporal lobe.

Another area of immediate investigation is to more clearly delineate the way crucial areas for different language functions are subdivided. We are now looking at action-object differences and differences based on semantic categories.

There are a large number of exciting issues related to the microelectrode recording. We are beginning to look at the role of changes in neural activity of various types (sustained, phasic, excitatory, inhibitory) in different locations for processes such as recent memory, by observing those changes with different memory loads. We have enough simultaneous recordings from different neurons now to investigate how the neural networks change with different behaviors, and individual items. And there is the question of patterns of activity with specific items. Of course, there are also many other aspects of behavior to investigate with these techniques—little has been done with visuospatial material for example.

There are many other areas to sample as the clinical opportunities for access present. For example, the role of striatal activity as recorded during placement of stereotaxic lesions or stimulators for dyskinesias. We will not run out of exciting questions to investigate with these techniques.

JOCN: Thank you.