Original article

□ Invasive recordings from human brain

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SUMMARY: *Awake neurosurgery for brain tumors and particularly epilepsy provides unique opportunities to investigate the neurophysiological correlates of human higher functions. This presentation reviews findings from single neuron recordings from lateral temporal cortex during language, recent verbal memory and verbal learning measures obtained in that setting. Changes in this activity with all these tasks are widespread, to both cerebral hemispheres, with the most widespread changes for learning, least for language tasks. Differences in activity between hemispheres, in different parts of dominant temporal lobe, and related to accuracy of performance on these tasks are discussed.*

KEY WORDS: *Human temporal cortex, Language, Learning, Memory, Single neuron activity.*

□ Registrazioni invasive per l'encefalo umano

RIASSUNTO: *La neurochirurgia a paziente sveglio per i tumori cerebrali e particolarmente per l'epilessia fornisce una opportunità unica di indagare i correlati neurofisiologici delle funzioni superiori. Questo articolo revisiona i risultati ottenuti in tale setting dalle registrazioni dell'attività dei singoli neuroni dalla corteccia laterale temporale durante il linguaggio, la memoria verbale recente e l'apprendimento verbale. I cambiamenti in tale attività con tutti questi compiti sono numerosi, in entrambi gli emisferi cerebrali, e quelli maggiori si verificano per l'apprendimento, almeno per il linguaggio. Si discutono le differenze nell'attività tra gli emisferi cerebrali, in parti differenti del lobo temporale dominante e in relazione all'accuratezza di come vengono eseguiti i compiti.*

PAROLE CHIAVE: *Corteccia temporale umana, Linguaggio, Apprendimento, Memoria, Attività del singolo neurone.*

□ INTRODUCTION

Awake neurosurgery provides a unique opportunity to investigate the neurophysiological basis of human cognition. In consenting patients, the Author has utilized this opportunity to investigate the neurophysiological correlates of language, recent verbal memory and verbal learning, in patients with medically refractory epilepsy undergoing temporal lobe resections with our awake surgical technique[10]. Those investigations have utilized several intraoperative techniques, including electrical stimulation mapping, optical imaging of the "intrinsic signal"[5] and extracellular recording of single neuronal activity. These techniques provide different perspectives on these cognitive processes. Stimulation mapping links a

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brain region to a cognitive process by interfering with that process. For language and memory, there is evidence that this effect predicts the effects of resection of that tissue[4,13,19] presumably then the activity of the tissue where interference is evoked, is crucial for the behavior, at least at that point in time. By contrast, optical imaging and recording of single neuron activity are physiologic changes correlated with the behavior, indicate where the physiologic activity is occurring, but not necessarily in tissue that is crucial for it. This article summarizes over two decades of investigations by the Author, investigations that have required collaboration between the Author and many associates from other disciplines, particularly neurophysiology and neuropsychology. Those collaborators are indicated in the authorship of the various publications describing the findings.

□ ELECTRICAL STIMULATION MAPPING: LANGUAGE

Classical lesion effects have established that the temporal lobe of the dominant hemisphere contains structures that are essential for language, verbal memory and verbal learning. Within dominant temporal lobe, language functions are usually related to lateral neocortex, particularly in posterior-superior temporal lobe, while recent verbal memory and learning effects are usually related to medial temporal structures, particularly hippocampus. Electrical stimulation mapping of lateral temporal neocortex of the dominant hemisphere also commonly produces interference in language measures. However, the sites of interference are often focal areas of 1 cm^2 or so, considerably smaller than the classic posterior temporal language area. Moreover, there is considerable individual variation in their location, including sites in anterior, superior and middle temporal gyri, well anterior to the classical posterior language region[21]. Moreover, as indicated in the Author's previous article (*at page 75*), temporal cortical stimulation frequently interferes with different language measures at different sites, including separate sites for naming in two languages[9,28] and naming compared to reading[16]. On the other hand, although temporal lobe is classically related to language perception, there has been little evidence from the Author's stimulation mapping studies of separation between sites where stimulation interferes with the sequential oro-facial motor functions involved in speech production, and speech perception[11]. These lateral temporal neocortical stimulation effects are lateralized, as stimulation of the non-language temporal cortex during naming usually does not evoke any interference[27].

□ ELECTRICAL STIMULATION MAPPING: RECENT VERBAL MEMORY AND LEARNING

Somewhat surprisingly, stimulation of lateral temporal neocortex has also interfered with performance on a recent verbal memory measure, particularly when the current is applied during encoding or storage of the verbal item. These sites have often been separate from those where stimulation interferes with naming of the same items, so that there appears to be separation of the crucial temporal cortical sites for recent verbal memory from those for language, even though the recent memory measure involved overt production of the name of the item to be encoded in memory[15,20]. Sites with interference in the memory measure were particularly likely in anterior temporal lateral neocortex. Resection of the sites with stimulation interference during the memory measure was associated with an increased postoperative verbal memory deficit[19]. In contrast to these lateral temporal cortical effects on recent verbal memory and to the classical effects of medial temporal lesions on memory, it has been difficult to show medial temporal or hippocampal stimulation interference on recent memory independent of evoking seizures[17]. Stimulation effects have also been compared between novel and overlearned items[29]. Interference was evoked from a wider area for novel items than for overlearned items, suggesting that the regions of brain crucial for learning are more extensive than those crucial to execution of a learned task.

□ OPTICAL IMAGING: LANGUAGE AND MEMORY

Optical imaging during language measures has shown changes in dominant temporal neocortex, but with a distribution wider than the sites of stimulation interference on the same language measure in the same subject[5]. In an unpublished case study, optical imaging changes in dominant temporal neocortex were also evident during a recent memory measure, but in a pattern different from that for naming. As in the reported cases, naming changes with optical imaging involved the sites where stimulation interfered with the same naming task, but were more widespread, while optical imaging changes during the recent memory measure spared the sites where stimulation had interfered with naming, but showed more intense involvement of more anterior temporal neocortex (*Haglund, Hochman and Ojemann, unpublished data*).

☐ SINGLE NEURON ACTIVITY: LANGUAGE

Extracellular recording of changes in single neuronal activity in lateral temporal cortex that correlate with language measures has shown substantial differences with the findings from stimulation mapping, likely reflecting the difference between a technique that shows where neurons are active and participating in a behavior from those regions that are essential for that behavior. Changes in single neuronal activity, compared to activity during control behaviors, occurred in equal proportions of neurons from dominant or non-dominant lateral temporal cortex for auditory word perception and repetition, visual object naming or word reading[1,2,22,30]. Changes with the auditory tasks were more frequently recorded than those with naming of visually presented objects or words.

Since dominance for language had been established in all subjects of these investigations, based on intracarotid amobarbital perfusion assessment (Wada test), changes in single neuron activity during the language tasks that lateralized to the dominant hemisphere were sought[30]. Two changes were identified. Changes in neuron activity can be relative increases (excitation) or relative decreases (inhibition) compared to the control measures. Relative inhibition during naming was one feature significantly lateralized to dominant hemisphere recordings. This relative inhibition may represent an inhibitory surround of a focal area of excitation elsewhere in temporal cortex, or perhaps the relation between temporal association cortex activity and subcortical activity is similar to that between motor cortex activity and spinal motor neuron activity, where the cortex modulates the greater subcortical excitation by changing the degree of inhibition. In a study of lateralized differences in neuron activity during a visuo-spatial task, inhibition was observed but lateralized to the non-dominant hemisphere[8], suggesting that the relative inhibition is a feature of dominance rather than specific to language tasks. The other language change lateralized to the dominant hemisphere was earlier activity. By contrast, non-dominant activity changes with language tended to be excitation late, at time of the speech output that was part of all the language tasks. In a few neurons, excitation during auditory word perception with inhibition during word production was demonstrated, even though the same words were heard aloud during both perception and production, but during production produced by the subject, during perception by another person[12]. Presumably this is part of the mechanism to prevent the sound of one's own voice from interfering with speech perception.

When several different language measures were administered during recording from the same neuron, the most common pattern was changes with only one task. This included changes during object naming compared to word reading[30] and changes with naming in only one of two languages[14]. Most of the changes in activity during language measures have been in the frequency of activity. However, recordings from a few neurons have had patterns of activity that appeared to be specific to specific words or to prosody[1].

☐ SINGLE NEURON ACTIVITY: RECENT VERBAL MEMORY

Recent verbal memory was assessed with a paradigm that separated encoding, storage and retrieval on each trial. Encoding was for object names, text words or auditory names. The subject was instructed to identify the item aloud and remember it. This was followed by a storage stage during which the subject had to remember the item while being distracted by having to identify several other items of a similar nature. This storage stage lasted between 9 s and 30 s in different studies. Retrieval was by recalling aloud the item presented during the encoding stage on that trial. Activity during the encoding stage was compared to that during identification of similar items, but without the instruction to remember them. Thus the two tasks differ only in that instruction, to remember the item or not. This instruction changed the frequency of activity in a large proportion of temporal neocortical neurons. In recordings from 239 neurons in 86 subjects, activity was significantly altered in 135 (57%)[6,18,22,23,24,31]. The proportion of neurons changing activity was similar in dominant and non-dominant temporal lobes.

Since temporal lobe representation of recent memory is usually related to medial structures, particularly hippocampus, we looked for evidence that this lateral temporal neocortical activity was specifically involved in recent memory. Three effects that are generally thought to modulate memory were examined - the effects on frequency of activity of increased memory load, of longer memory storage and of memory errors. Memory load was assessed for encoding of 1 or 5 items in recordings from 80 neurons in 10 subjects. Of the 31 neurons related to recent memory by changes between identification and recent memory encoding, 58% had changes with load. Duration of storage was assessed for 10 s or 30 s in the same recordings. Forty-eight percent of those neurons changed activity with the increased storage time (*Zamora, Corina, and Ojemann, unpublished data 2008*). In a separate study involving recordings during recent memory from 113 neurons in 26 subjects, nine neurons were identified that had changes in activity that significantly differentiated correct from incorrect memory performance[25]. All neurons making this discrimination did so during encoding, so that changes in neuron activity indicated an error before recall performance indicated that error. Unexpectedly, these neurons had a significant tendency to be localized to superior temporal gyrus and adjacent superior middle temporal gyrus. The changes in activity differentiating correct from incorrect performance included changes in frequency of both encoding excitation and inhibition. Considered together, these studies provide evidence that at least some of the changes in neuron activity recorded in lateral temporal neocortex during recent memory measures have properties indicating that they participate in memory mechanisms.

The patterns of change in activity during the memory task provide the basis for a model of the roles of temporal cortex in recent verbal memory[24,26]. Activity patterns were divided based on changes between encoding-storage-recall stages, and on the timing of changes during encoding, in both situations compared to activity during identification of the same items without the memory instruction. Activity during different stages of the memory task was divided between that sustained through the stages, and that occurring only with one stage. Sustained activity was present throughout lateral temporal cortex, but represented a larger proportion of activity in middle temporal gyrus[22,24]. This activity change has been modelled as reflecting attentional mechanisms. Activity changing with only one stage was significantly more frequent in recordings from basal temporal cortex including inferior temporal and fusiform gyri, perhaps a pattern more specific to memory mechanisms.

Changes in activity during encoding were also present throughout lateral temporal neocortex. This was divided into that occurring early, during perception and processing of the items to be encoded, late, related to the overt speech output associated with encoding, or sustained throughout encoding[26]. Early activity was significantly more likely in superior temporal gyrus. The timing of the average peak of this activity in superior temporal gyrus recordings was 310 ms, compared to 680 ms for early activity recorded in middle temporal gyrus. Some of the anterior superior temporal gyrus activity peaked very early, within 150 ms after item presentation, some within 50 ms. The peak of the visual evoked potential in human occipital cortex is about 55 ms[3], so signal related to the encoded item is apparently increasing activity in some anterior temporal neurons simultaneously with the arrival of the signal in primary visual cortex. Middle temporal gyrus activity not only tended to peak later during perception and processing phase of encoding, but also was significantly more likely to show activity related to overt speech output. That activity most often occurred within the 300 ms immediately preceding the onset of the overt speech. The model of dominant lateral cortical excitatory activity during recent memory encoding derived from these observations includes early perceptual changes in superior temporal gyrus and later processing and output changes in middle gyrus. Note that these changes are specific to recent memory, and not to identification without the memory instruction. Activity sustained throughout encoding was widely recorded from lateral cortex. However, that recorded from the superior and middle thirds of middle temporal gyrus was significantly more likely to represent relative inhibition (compared to identification without the memory instruction) than that recorded from surrounding cortex. Relative inhibition during speech output was present in recordings from a portion of this same middle temporal gyrus. About 10% of the 98 neurons included in this study of timing of activity during encoding had a pattern suggesting a simultaneous convergence of sustained tonic activity, perhaps representing an attentional effect specific to the task but not the item, and phasic activity during early perception and processing, more likely item specific. Simultaneous convergence of inputs to a neuron has been proposed as a mechanism for memory with potentiation of synaptic inputs to a neuron[7].

☐ SINGLE NEURON ACTIVITY: LEARNING

Learning was assessed with a word pair association paradigm, where the same 20 words (concrete nouns) were used under three conditions - identification of the words, as the items to be encoded in recent memory, and as 10 unrelated word pairs. The word pairs were presented in a series of trials, each trial including a presentation of each pair, which the subject read aloud, and a test of learning of each pair, with the first word presented, which the subject read and then gave the second word, if learned. These measures have been used in two studies[23,31]. In one study, activity was significantly changed by word reading in 36% of neurons, by memory encoding in 77%, and by the learning task in 100% of the recorded neurons. Changes in activity that discriminated learned from unlearned pairs on the first presentation trial were identified. These changes occurred in neurons that were inhibited by the word reading task but excited by memory encoding. The activity change that discriminated learned from unlearned pairs in these neurons was significantly increased activity sustained during and after the word pair was correctly read on that first presentation trial[23]. Whether this sustained activity represents continued rehearsal of the pairs that are learned, or reflects tonic activity associated with attentional mechanism is unknown.

Once the association was learned, the level of activity began to decrease, beginning the second trial after the pair was learned[31]. Subjects who learned the pairs readily had significantly greater activity in neurons also related to overt word reading than did subjects who learned words poorly. Conversely the early learners had less activity in neurons unrelated to identification or memory than the poor learners. Thus these neuronal events seem to be essential for learning. Based on these studies the neural events in temporal cortex during verbal associative learning have been modelled as a transient sustained increase in activity during encoding of the association, activity sustained after identification of the pair, but rapidly declining within a few trials after initial learning, so that later retrieval of the association requires activity in many fewer neurons. Indeed there is the suggestion that for overlearned items, some of those neurons may be actively inhibited. Note that these findings with single neuron recording of less activity for overlearned items are similar to the findings with stimulation mapping indicated above, of smaller crucial areas for overlearned items.

☐ REFERENCES

1. Creutzfeldt O., Ojemann G., Lettich E.: Neuronal activity in the human lateral temporal lobe. I. Responses to speech. Exp Brain Res 1989; 77 (3): 451-475.
2. Creutzfeldt O., Ojemann G., Lettich E.: Neuronal activity in the human lateral temporal lobe. II. Responses to the subjects own voice. Exp Brain Res 1989; 77 (3): 476-489.
3. Farrell D.F., Leeman S., Ojemann G.A.: Study of the human visual cortex: direct cortical evoked potentials and stimulation. J Clin Neurophysiol 2007; 24 (1): 1-10.
4. Haglund M.M., Berger M.S., Shamseldin M., Lettich E., Ojemann G.A.: Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery 1994; 34 (4): 567-576.
5. Haglund M.M., Ojemann G.A., Hochman D.W.: Optical imaging of epileptiform and functional activity in human cerebral cortex. Nature 1992; 358 (6388): 668-671.
6. Haglund M.M., Ojemann G.A., Schwartz T.W., Lettich E.: Neuronal activity in human lateral temporal cortex during serial retrieval from short-term memory. J Neurosci 1994; 14 (3 Pt. 2): 1507-1515.
7. Hebb D.O.: The Organization of Behavior. Wiley, New York, 1949.
8. Lucas T.H. Jr., Schoenfield-McNeill J., Weber P.B., Ojemann G.A.: A direct measure of human lateral temporal lobe neurons responsive to face matching. Brain Res Cogn Brain Res 2003; 18 (1): 15-25.
9. Lucas T.H. 2nd, McKhann G.M. 2nd, Ojemann G.A.: Functional separation of languages in the bilingual brain: a comparison of electrical stimulation language mapping in 25 bilingual patients and 117 monolingual control patients. J Neurosurg 2004; 101 (3): 449-457.
10. Ojemann G.A.: Awake operations with mapping in epilepsy. In: H. Schmidek, W. Sweet (editors). Operative neurosurgical techniques (3rd edition). Saunders, Philadelphia, 1995: 1317-1322.
11. Ojemann G.A.: Brain organization for language from the perspective of electrical stimulation mapping. Behav Brain Sci 1983; 2: 189-206.
12. Ojemann G.A.: Cortical organization of language and verbal memory based on intraoperative investigations. Prog Sensory Physiol 1991; 12:193-230.
13. Ojemann G.A.: Electrical stimulation and the neurobiology of language. Behav Brain Sci 1983; 6: 221-230.

14. Ojemann G.A.: Organization of language cortex derived from investigations during neurosurgery. Semin Neurosci 1990; 2:297-305.
15. Ojemann G.A.: Organization of short-term verbal memory in language areas of human cortex: evidence from electrical stimulation. Brain Lang 1978; 5 (3): 331-340.
16. Ojemann G.A.: Some brain mechanisms for reading. In: C. Von Euler, I. Lundberg, G. Lennerstrand (editors). Brain and reading. MacMillan Press Ltd, Hampshire, 1989: 47-59.
17. Ojemann G.A., Creutzfeldt O.D.: Language in humans and animals: Contribution of brain stimulation and recording. In: V. Mountcastle, F. Plum, S. Geiger (editors). Handbook of physiology. The nervous system V. Higher functions of the brain. Williams and Wilkins, Baltimore, 1987: 675-699.
18. Ojemann G.A., Creutzfeldt O., Lettich E., Haglund M.M.: Neuronal activity in human lateral temporal cortex related to short-term verbal memory, naming and reading. Brain 1988; 111 (Pt. 6) 1383-1403.
19. Ojemann G., Dodrill C.: Intraoperative techniques for reducing language and memory deficits with. left temporal lobectomy. Adv Epileptol 1987; 16: 327-330.
20. Ojemann G.A., Dodrill C.B.: Verbal memory deficits after left temporal lobectomy for epilepsy. Mechanism and intraoperative prediction. J Neurosurg 1985; 62 (1): 101-107.
21. Ojemann G., Ojemann J., Lettich E., Berger M.: Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989; 71 (3): 316-326.
22. Ojemann G.A., Schoenfield-McNeill J.: Activity of neurons in human temporal cortex during identification and memory for names and words. J Neurosci 1999; 19 (13): 5674-5682.
23. Ojemann G.A., Schoenfield-McNeill J.: Neurons in human temporal cortex active with verbal associative learning. Brain Lang 1998; 64 (3): 317-327.
24. Ojemann G.A., Schoenfield-McNeill J., Corina D.P.: Anatomic subdivisions in human temporal cortical neuronal activity related to recent verbal memory. Nat Neurosci 2002; 5 (1): 64-71.
25. Ojemann G.A., Schoenfield-McNeill J., Corina D.: Different neurons in different regions of human temporal lobe distinguish correct from incorrect identification or memory. Neuropsychologia 2004; 42 (10): 1383-1393.
26. Ojemann G.A., Schoenfield-McNeill J., Corina D.: The roles of human lateral temporal cortical neuronal activity in recent verbal memory encoding. Cereb Cortex 2009; 19 (1): 197-205.
27. Ojemann G.A., Whitaker H.A.: Language localization and variability. Brain Lang 1978; 6 (2): 239-260.
28. Ojemann G.A., Whitaker H.A.: The bilingual brain. Arch Neurol 1978; 35 (7): 409-412.
29. Ojemann J.G., Ojemann G.A., Lettich E.: Cortical stimulation mapping of language cortex by using a verb generation task: effects of learning and comparison to mapping based on object naming. J Neurosurg 2002; 97 (1): 33-38.
30. Schwartz T.H., Ojemann G.A., Haglund M.M., Lettich E.: Cerebral lateralization of neuronal activity during naming, reading and line-matching. Brain Res Cogn Brain Res 1996; 4 (4): 263-273.
31. Weber P.B., Ojemann G.A.: Neuronal recordings in human lateral temporal lobe during verbal paired associate learning. Neuroreport 1995; 6 (4): 685-689.